~~Confidential~~

Helsinki, 16 November 2021

Addressees
Registrant(s) of TPSA_C12-ASA_JS as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
17/06/2014

Registered substance subject to this decision ("the Substance")
Substance name: Dihydro-3-(tetrapropenyl)furan-2,5-dione
EC number: 247-781-6
CAS number: 26544-38-7

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed in C.1, by the deadline of ***21 February 2023*** and for all other information listed below by ***21 August 2025***.

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

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

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

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

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

1. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)

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

3. Simulation testing on ultimate degradation in surface water (triggered by Annex VIII, Section 9.2.)

4. Soil simulation testing (triggered by Annex VIII, Section 9.2.)

5. Sediment simulation testing (triggered by Annex VIII, Section 9.2.)

6. Identification of degradation products (triggered by Annex VIII, Section 9.2.)

7. Bioaccumulation in aquatic species (triggered by Annex I, Sections 0.6.1. and 4; Annex XIII, Section 2.1.)

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. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

6. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: EU C.23./OECD TG 307) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: EU C.24./OECD TG 308) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

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

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

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

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

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

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

Information required depends on your tonnage band

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

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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. The same information requirement may therefore be listed under several of the sections (A-D) in the above. This relates to the different requirements under the REACH Annexes for this information (see the reasons in the following Appendices); it does not mean that multiple studies are requested. 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 entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes".

Appeal

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

Failure to comply

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

Authorised[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 adaptation under Annex XI, Section 1.2**

You seek to adapt the following information requirements by applying a weight of evidence approach under Annex XI, Section 1.2.:

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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

Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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 adaptation.

For the repeat dose toxicity, you have indicated that "*A chemical category member, tripropenyl succinic anhydride (TSA) was tested in a 28-day repeated dose toxicity study (OECD 421) in Wistar rats, at doses of 50, 150 and 250 mg/kg bw/day, in a corn oil vehicle. The NOAEL was 50 mg/kg bw/d. There is also a 14 -day dose range finding study on the registered substance, tetrapropenyl succinic anhydride (TPSA). No significant toxicity was found at doses up to 300 mg/kg bw/d. The WHO reviewed the human health risks of cyclic acid anhydrides, and, while data are limited, did not find a weight of evidence which suggests that repeated dose exposure confers a toxicity risk*."

For the reproductive toxicity including developmental toxicity, you have indicated that "*No reproductive effects were observed in parental reproductive organs or performance after exposure to this anhydride [TSA], a member of the C8-C12 alkenyl succinic anhydride category. The general NOAEL was 50 mg/kg bw/d for body weight effects; the NOAEL for reproductive effects could be higher. No adverse effects were observed in offspring at the highest dose tested in an OECD 421 guideline study under GLP. The WHO reviewed the human health risks of cyclic acid anhydrides, and, while data are limited, did not find a weight of evidence which suggests reproductive toxicity risk*.".

Whilst this can be regarded as integrated summary of the information to support your adaptation, you have not included an assessment, integration and weighing of the individual sources of information for relevance, reliability, coverage, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study. Irrespective of the above mentioned deficiency on the documentation, which in itself could

lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Your weight of evidence approach has the following deficiencies that are common to all information requirements under consideration.

Reliability of the provided information with analogue substances

You intend to predict the toxicological properties of the Substance for the listed above information requirements from information obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to be considered reliably contribute to the weight of evidence, it would thus have to meet the requirements for Grouping of substances and read-across approach.

Annex XI, Section 1.5. for Grouping of substances and read-across approach 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].

You have used information from two categories as part of the source of information used in your weight of evidence approaches:

- 'C8-12 Alkenyl Succinic Anhydride' category approach (I); and
- 'Cyclic acid anhydrides' category approach (II).

We have evaluated the two categories provided as sources of information and identified the following shortcomings as explained below.

I. 'C8-12 Alkenyl Succinic Anhydride' category approach

I.1 Scope of the grouping

I.1.1 Description of the grouping for 'C8-12 Alkenyl Succinic Anhydride' category

In your registration dossier you have formed a group (category) called the 'C8-12 Alkenyl Succinic Anhydride' category. You have provided a read-across justification document in IUCLID under the relevant endpoint study records.

For the purpose of this decision, the following abbreviations are used for the group members:
[1] TPSA 3-dodecenyl dihydrofuran-2,5-dione (EC No. 247-781-6), referred to as "the Substance" thereafter;
[2] OSA 3-oct-2-en-1-yl dihydrofuran-2,5-dione (EC No. 629-679-7);
[3] n-DDSA 3-dodec-2-en-1-yl dihydrofuran-2,5-dione (EC No. 243-296-9)
[4] TSA 3-nonenyldi hydrofuran-2,5-dione (EC No. 295-556-6).

You define the the structural basis for the grouping as

[2] ECHA Guidance R.6: QSARs and grouping of Chemicals

"*Common functional groups are:*
a) Dihydro-2,5-Furandione (cyclic anhydride) ring
b) Carbon chain of length 8 to 12 carbons, with or without branching alkyl groups
c) A single double bond in the carbon chain, location unspecified
d) The category substances do not have additional functional groups which could introduce additional toxicities.".

ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

I.1.2 Assessment of the grouping

ECHA notes the following shortcomings with regards to your grouping approach.

Applicability domain of the category

According to the ECHA Guidance, a category (grouping) hypothesis should address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint".*[3] Particularly, "*the applicability domain of a (sub)category would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members*".[4] Therefore, to reliably predict properties within a category the applicability domain should be described including the borders of the category, for which chemicals the category does not hold and a justification for the inclusion and/or exclusion rules.

You describe the applicability domain of the substances by common functional groups within the group members. In addition, you specify that the category members do not have additional functional groups which could introduce additional toxicities.

While common structural features are presented, you do not introduce a set of exclusion rules that identify the allowed variations on some elements of the structures of the category members. For instance, the criteria for alkyl chain branching does not specify the type and extent of allowed branching within the group whereas this parameter is expected to impact physico-chemical, environmental fate, and (eco)toxicological properties.

Therefore, the applicability domain does not introduce unambiguous exclusion criteria that identify all the allowed structural variation and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members.

I.2 Predictions for toxicological properties

You have provided the following reasoning for the prediction of (eco)toxicological properties: *"The hypothesis is that data can be read-across among members of the category because their properties and behaviours are similar, based on common functional groups and similar breakdown products, and based on a constant pattern in the changing of the potency of the carbon chain length on the molecules".*

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 based on an identified trend within the group.

[3] ECHA Guidance R.6: Section R.6.2.4.1.
[4] ECHA Guidance R.6: Section R.6.2.1.2.

For the repeated dose toxicity and for pre-natal developmental toxicity study, you have provided information for the category member TSA, referred to as the source substance thereafter.

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

I.2.1 Characterisation of the group members

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of chemical similarity may be considered as group*."

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed"*, and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s).[5] Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

Furthermore, whenever the Substance or the source substances are UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances qualitative compositional information of the individual constituents of the substances needs to be provided; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[6]

You provide a description of the group members in the read-across justification document. You indicate that two group members (OSA [2] and n-DDSA [3]) are multi-constituent substances and that two are UVCBs (TPSA [1] and TSA [4]).

While the detailed description of the multi-constituent group members are provided, you state for the UVCBs that: '*The main components of TPSA are the* [redacted]*, which is itself a UVCB. The* [redacted] *is C12 rich, with this fraction usually accounting for* [redacted]*% or more of the total reactant mixture, as obtained from fingerprinting of this material by suppliers. The TPSA reaction product with this material reflects the same proportion of carbon side chains attached to succinic anhydride. In a similar manner, TSA is reacted with a C9-rich UVCB material. Designation of impurities is not indicated for UVCB substances (TPSA and TSA).*'

While you describe that the UVCB group members are C9 or C12 rich, you have not characterised these substances by compositions based on the alkyl chain distribution and branching, nor have you provided concentration ranges for each of the carbon number moieties.

In the absence of this information, no qualitative or quantitative comparative assessment of the compositions of the category members can be completed.

Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

[5] ECHA Guidance R.6: Section R.6.2.3.1.
[6] ECHA Guidance R.6: Section R.6.2.5.5.

I.2.2 Data density across the category to support the claimed trends

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.*

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[7] To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

The substances within the category have variations in the alkenyl moiety of the common 2,5-furandione ring, differing in length of the carbon chain and being either branched or linear. You have indicated that the potency differences between the substances could be explained by the length of the carbon chain. In addition, you stated that "*steric hindrance of the branched chains may occur, whereas linear chains may be accessible to enzymes or membrane components. The branched chains may also be less flexible than linear chains*.".

You have provided experimental information only for two category members. Experimental data is available for the Substance (14-day dose range finding (DRF) study) and the category member TSA (OECD TG 421) with branched alkenyl chain within the common dihydro-2,5-furandione (cyclic anhydride) ring.

In addition, in your read-across justification document you have provided structural alert profiles using the QSAR Toolbox for all category members and refer to the assessments of Alkyl Alcohols C6-C13, Alkyl Acetate (C6-13) as well as Aliphatic Esters categories.

The information from the QSAR predictions may indicate that the structural differences within the category members do not influence the reactivity of the substances. However, due to the complexity of the systemic interactions as well as the large number of targets/mechanisms associated with repeated dose and reproductive (including developmental) toxicity, the information from the computational tools need to be supported by further experimental data.

The experimental information is available only for two substances in the category, which is not sufficient to establish a trend across the category. In addition, the available information does not allow adequate comparison of the substance properties. While both 14-d DRF with the Substances and the OECD TG 421 with the source substance provide some information on the target organ toxicity, the DRF does not provide any information on developmental toxicity properties of the Substance.

You also refer to the Alkyl Alcohols C6-C13, Alkyl Acetate (C6-13) or Aliphatic Esters categories. These categories do not provide information for the Substance or for the other category members and you have not explained how, other than referring to the carbon chain length and branching, these substances can be used to support the predictions within the category.

Based on above, you have not provided adequate information, covering the range of structural variations, to allow comparison of the properties of the substances in your category and to allow conclusion of that the toxicological properties of the substances following repeated exposure (including reproductive toxicity) are likely to follow a regular pattern.

[7] ECHA Guidance R.6: Section R.6.2.1.5.

I.3 Conclusion for predictions based on 'C8-12 Alkenyl Succinic Anhydride' category

Based on above, the information from the analogue substances included in 'C8-12 Alkenyl Succinic Anhydride' category does not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

II. 'Cyclic acid anhydrides' category approach

II.1 Scope of the grouping

In your registration dossier you have provided information on a group of 'cyclic acid anhydrides' and attached a Concise international chemical assessment document (CICAD, 2009) on Cyclic acid anhydrides category in IUCLID Section 13.

For this category, you have provided information on the trimellitic anhydride (CAS 552-30-7), phthalic anhydride (CAS No. CAS 85-44-9), succinic anhydride (CAS 108-30-5) and maleic anhydride (CAS 108-31-6) under the endpoint study records. This document does not have any information on the Substance. Therefore, ECHA considers that you have provided information on studies conducted with other substances than your Substance as part of the weight of evidence approach intended to identify the hazards of the Substance.

ECHA notes the following shortcomings with regards to your grouping approach.

Absence of read-across justification

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[8]

In the dossier, you have provided a 'cyclic acid anhydride' category document (CICAD, 2009) containing hazard information on various cyclic acid anhydrides.

The documentation that you provided does not contain any specific justification whereby relevant hazard properties of the Substance may be predicted from data available for some of the substances included in the 'cyclic acid anhydride' category. Specifically, your dossier does not:

- include robust study summaries of the underlying studies on the analogue substances that you consider relevant for this weight of evidence approach; and
- explain how and why such information can contribute to the identification of the properties of the Substance.

In the absence of this information, ECHA cannot verify that the information from the substances included in the 'cyclic acid anhydride' category can reliably contribute to the weight of evidence approach properties intended to identify the properties of the Substance.

II.2 Conclusions on the predictions based on ''*Cyclic acid anhydrides'* category

Based on above, the information from the analogue substances included in 'Cyclic acid anhydrides' category does not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

[8] ECHA Guidance R.6: Section R.6.2.6.2

Conclusion on the reliability of the information on analogue substances

Based on the information in the dossier, 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.

2. Assessment of your Annex XI, Section 2 'Testing technically not possible' adaptation

You also seek to adapt the information for the following standard information requirements, because you consider testing technically not possible:

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

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

Annex XI, Section 2 states that the study may be omitted if it is technically not possible to conduct the study as a consequence of the properties of the substance. The guidance given in the test methods referred to in Article 13(3), more specifically on the technical limitations of a specific method, shall always be respected.

OECD TG 414 specifies that "*If a vehicle or other additive is used to facilitate dosing, consideration should be given to the following characteristics: effects on the absorption, distribution, metabolism, and retention or excretion of the test chemical*" and that "*The test chemical or vehicle is usually administered orally by intubation. If another route of administration is used, the tester should provide justification and reasoning for its selection, and appropriate modifications may be necessary*".

In addition, ECHA guidance[9] specifies that for reproductive toxicity studies that "*the oral route (gavage, in diet, or in drinking water) is the "default" route, except for gases*".

You have provided a hydrolysis study (OECD TG 111) for the Substance. Based on this, you consider that "*The substance has been documented to be unstable in aqueous buffers*".

Oral route is the 'default' route for the developmental toxicity study and, while in the developmental toxicity study the test chemical is usually administered orally by intubation, the test substance can also be delivered in diet. You indicated that in the aqueous buffer, the substance is not stable, however, you have not provided any considerations on the possibility to administer the Substance in diet.

Furthermore, while you have considered the testing and the stability of the Substance in the aqueous buffer, you have not provided any information on the stability of the Substance in other vehicles.

As you have not considered testing via dietary route or by using other than aqueous vehicle, you have not demonstrated that it would not be technically possible to conduct the study. Therefore, your adaptation under the Annex XI, section 2 is rejected.

3. Information from your comments to the draft decision

3.1 New read-across approach in accordance with Annex XI, Section 1.5

[9] ECHA Guidance R.7a, Section R.7.6.2.3.2 Procedure for adaptations and testing approaches

In your comments on the initial draft decision you have submitted a new proposal for read-across approach in accordance with Annex XI, Section 1.5 for the following endpoints:

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- 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.)
- Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)
- Soil simulation testing (Annex IX, Section 9.2.1.3.)
- Sediment simulation testing (Annex IX, Section 9.2.1.4.)
- Identification of degradation products (Annex IX, 9.2.3.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

In your comments to the draft decision, you do not agree to perform the requested studies with the Substance. Instead, you intend to provide a new read-across adaptation according to Annex XI, Section 1.5 'Grouping and read-across', of the REACH Regulation.

You propose to predict the (eco)toxicological properties of the Substance from studies on the source substance tetrapropenyl succinic acid (TPS acid) [EC No. 248-698-8, CAS No. 27859-58-1], which is obtained from direct hydrolysis of the Substance.

In the comments, you present a strategy relying on

- existing studies on the source substance for the following endpoints: Short-term repeated dose toxicity (28 day), Short-term toxicity testing on aquatic invertebrates, Growth inhibition study aquatic plants, Short-term toxicity testing on fish, Long-term toxicity testing on aquatic invertebrates;
- studies yet to be conducted for the source substance, which have been requested by ECHA in a separate compliance check decision, for the following endpoints: Sub-chronic toxicity study (90-day), Pre-natal developmental toxicity study, Simulation testing on ultimate degradation in surface water, Soil simulation testing, Sediment simulation testing, Identification of degradation products, Bioaccumulation in aquatic species;
- a detailed comparative identity and characterisation of both the Substance and the source substance;
- development and validation of suitable analytical methods for these 'difficult to test' substances;
- further (bridging) studies where considered necessary;
- update on the dossier robust study summaries to include full scientific justification of the read-across validity for each endpoint;
- update on the chemical safety assessment (CSA) to further clarify potential risks;
- existing information on the hydrolysis of acid anhydrides together with generation of further data to adequately demonstrate the (bio)transformation of TPSA to TPS acid;

However, you have not provided any of the proposed new information. Therefore, as this strategy relies on a read-across approach that has not yet been fully described and justified, as well as on data which is yet to be generated for the proposed source substance and the Substance (including bridging studies and supporting information), no conclusion on the compliance of the proposed adaptation can be made.

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

1. Short-term aquatic toxicity to invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).
1.1 Information provided in the registration dossier to fulfil the information requirement:

- OECD TG 202 ([redacted] 2013) key study with TSA used as the source substance in a read across approach;
- a read-across justification document in IUCLID Section 13.

1.2 Assessment of your read-across approach provided in the registration dossier under Annex XI, Section 1.5.

You seek to adapt the standard information requirement for Short-term toxicity testing on aquatic invertebrates (Annex VII, REACH Section 9.1.1.). by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5.

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach 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 (addressed under 'Scope of the grouping'). 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[10,11].

A. Scope of the grouping

In your registration dossier you have formed a group (category) called the 'C8-12 Alkenyl Succinic Anhydride Category' as previously described in Appendix on 'Reasons common to several requests', Section A.I.1. ECHA's assessment of your grouping approach has already been provided in Appendix on 'Reasons common to several requests', Section A. I.1.2 and the conclusions also apply to this endpoint.

B. Predictions for ecotoxicological properties

You have provided a read-across justification document for the 'C8-12 Alkenyl Succinic Anhydride Category'. Under the endpoint study record for the relevant endpoint you provide a summary of the read-across justification as follows:

'*The hypothesis for the category of C8-12 Alkenyl Succinic Anhydrides is that data can be read-across among members of the category, because the properties and behaviours of*

[10] Read-Across Assessment Framework (RAAF). 2017 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)
[11] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 Available online: https://doi.org/10.2823/794394

category members are similar, based on common functional groups, similar breakdown products, and demonstration of a constant pattern associating the potency of properties with the various carbon chain lengths"

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 based on an identified trend within the group.

ECHA notes the following shortcoming(s) with regards to prediction of ecotoxicological properties.

Characterisation of the group members

Annex XI, Section 1.5 of the REACH Regulation provides that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of chemical similarity may be considered as group*."

According to the ECHA Guidance, "*the purity and impurity profiles of the substance and the structural analogue need to be assessed"*, and "*the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded*". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s).[12] Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

Furthermore, whenever the Substance and/or the source substances) are UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances qualitative compositional information of the individual constituents of the substances needs to be provided; as well as quantitative characterisation in the form of information on the concentration of the individual constituents of these substances; to the extent that this is measurable.[13]

You provide a description of the group members in the read-across justification document. You indicate that two group members (OSA [2] and n-DDSA [3]) are multi-constituent substances and two are UVCBs (TPSA [1] and TSA [4]).

While the detailed description of the multi-constituent group members are provided, you state for the UVCBs that: '*The main components of TPSA are the* [redacted] *which is itself a UVCB. The* [redacted] *is C12 rich, with this fraction usually accounting for* [redacted]*% or more of the total reactant mixture, as obtained from fingerprinting of this material by suppliers. The TPSA reaction product with this material reflects the same proportion of carbon side chains attached to succinic anhydride. In a similar manner, TSA is reacted with a C9-rich UVCB material. Designation of impurities is not indicated for UVCB substances (TPSA and TSA).*'

You describe that the UVCB group members are C9 or C12 rich, but you have not characterised these substances by compositions based on the alkyl chain distribution and branching, nor have you provided concentration ranges for each of the carbon number moieties.

In the absence of this information, no qualitative or quantitative comparative assessment of the compositions of the category members can be completed.

[12] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.3.1
[13] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.5.5

Therefore, ECHA considers that it is not possible to assess whether the attempted predictions are compromised by the composition of the source substance.

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*"[14]. 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 other category members.

Supporting information must include information to confirm that the Substance and the members 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 category members cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the category members 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 category members.

To support your hypothesis "*a constant pattern in the changing of the potency of the carbon chain length on the molecules*, you have provided following information:

- Alert profiles using the QSAR Toolbox

For (eco)toxicological endpoints, you have determined structural characteristics (chemical functionality and structural similarity) and mechanistic alerts using the QSAR Toolbox v2.1 for the Substance and for the category members.

You indicate that "*The members of this proposed category demonstrate the same mode of action, as identified by the OECD (Q)SAR Toolbox Profiling tools (Version 2.1, 2011).*".

- Information from experimental studies as provided in the data matrix:

- Short term invertebrate toxicity (OECD 202) with TSA [4]
- Short term fish toxicity studies (OECD 203), three with TPSA [1] and one with TSA [4]
- Algal toxicity (OECD 201) with TPSA [1]
- Water solubilities and Log Kow for all group members, with the exception of TSA [4].

In addition, we note the following additional information is available in the TSA dossier that was omitted from the data matrix:
- Algal toxicity (OECD 201) with TSA [4]
- Water solubility and Log Kow for TSA [4]

We have assessed the available data and concluded that this information does not allow ECHA to verify crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members. This conclusion is based on the following reasons:

[14] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

- Alert profiles using the QSAR Toolbox

The similarity in presence or absence of structural alerts may indicate that structural differences between the category members do not influence the reactivity of the substance e.g. on the protein or DNA. However, you do not provide any QSAR data specific to aquatic toxicity endpoints to assess how structural differences may influence ecotoxicity endpoints.

Therefore, the QSAR information provided can be used to support the prediction, but it does not provide quantitative comparison of ecotoxicological properties of the substances on its own. The QSAR data provided in the dossier provides minimal supporting information for the prediction of aquatic toxicity.

- Information from experimental studies

You have compared physico-chemical parameters for three of the group members including water solubility and Log Kow.

In the data matrix you provide the following water solubilities for group members: TPSA [1] 21.34 mg/L; OSA [2] 20 mg/L; and, nDDSA [3] 0.13 mg/L.

You also provide the following values for Log Kow in the data matrix: TPSA [1] ≥4.39; OSA [2] ≥4.68; and, nDDSA [3] 4.38 & 5.

We further note that the water solubility for TSA [4] is 0.9 ± 0.09 g/L and the Log Kow for TSA [4] is 2.79.

There are significant differences in water solubilities and Log Kow between the Substances in the group. These key physico-chemical differences in water solubility and Log Kow must be considered when predicting environmental fate and ecotoxicity endpoints. These physico-chemical differences, and the potential impact on aquatic toxicity, are not addressed in the read across justification documentation.

Furthermore, the influence of the differing structure and physicochemical properties on the predicted ecotoxicological properties cannot be assessed in the absence of aquatic toxicity data across the category. There is no aquatic toxicity data for any species for OSA [2] and DDSA [3].

There are acute fish and algae data for TPSA [1]. However, these studies have critical methodological deficiencies. Key issues include the lack of analytical monitoring to confirm exposure concentrations. Considering the high partition coefficient of the substances, the substances are difficult to test and maintain in the test media. Therefore, in the absence of analytical monitoring, the results of these studies cannot be considered reliable. Reliable aquatic toxicity data is therefore available for only one substance in the category (TSA, [4]) hence the aquatic toxicity cannot be compared across the group.

Relevant, reliable and adequate information from bridging studies, providing comparative data confirming that the substances cause the same type of effects, is therefore lacking.

In conclusion, you have not provided sufficient supporting information to confirm that the group members have similar (eco)toxicological properties and that the structural differences would not affect the predicted properties of the substances.

C. Conclusions on the grouping of substances and read-across approach based on 'C8-12 Alkenyl Succinic Anhydride Category'

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substances in the 'C8-12 Alkenyl Succinic Anhydride Category' approach. 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.

1.3 Information from your comments to the draft decision to fulfil the information requirement:

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of a new grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Study design

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. The Substance is difficult to test based on low water solubility (10-20 mg/L), high partition coefficient (Log Kow>4.38), surface activity (surface tension of 28.6 nM/m provided in the dossier) and ionisable properties. OECD GD 23 indicator values for difficult to test substances are Log Kow >4, saturation concentration in aqueous media expected to be <100 mg/L and surface tension <60 mN/m. 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 solution.

If analytical monitoring of exposure concentrations is not technically feasible, a justification must be provided. This justification should confirm that the analytical methods attempted were state of the art and include a justification as to why detection lower limits were not feasible (any preliminary analytical efforts should also be described in the report).

For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (ECHA Guidance,

Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);
- prepare WAFs separately for each dose level (i.e. loading rate) and in a consistent manner.

2. Growth inhibition study aquatic plants

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

You have provided the following information in your registration dossier:

- OECD TG 201 study with the Substance ([redacted], 1997)

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- The results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- if the test material is tested at the saturation concentration, evidence must be provided that all reasonable efforts have been taken to achieve a saturation concentration, which include: (1) an analytical method validation report demonstrating that the analytical method is appropriate, and (2) the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution;
- 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. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided. This justification should confirm that the analytical methods attempted were state of the art, and include a justification as to why detection lower limits were not feasible (any preliminary analytical efforts should also be described in the report);
- chemical specific analysis of the test solutions is required to demonstrate stability of exposure concentrations during the test;
- 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;

Your registration dossier provides an OECD TG 201 showing the following:
- Tabulated data on the algal biomass determined daily for each treatment group and control are not reported and you have not specified whether the study meets the validity criteria specified in the test guideline (i.e. section-by-section growth rates in the control cultures; the increase in biomass during the test period; the mean coefficient of variation for section-by-section specific growth; and the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures);

- No analytical method validation report or results of a preliminary solubility experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution are provided;
- You state in the dossier that analytical monitoring was not conducted. You do not provide detailed justification for why the analytical monitoring of exposure concentrations is not technically feasible, including the methods attempted, confirmation that these were state of the art, or details of the results obtained from these efforts;
- No analytical monitoring was conducted to confirm exposure concentrations;
- You based the EC50 on nominal concentrations, but you did not demonstrate that concentration of the test material was maintained within 20% of the nominal or measured initial concentration throughout the test.

Based on the above,

- in the absence of tabulated data on the algal biomass determined daily, the reporting of the study is not sufficient to conduct an independent assessment of its reliability and determine if the validity criteria of OECD TG 201 are met.

Furthermore, the Substance is difficult to test (based on OECD GD 23 indicator values of Log Kow >4, saturation concentration in aqueous media expected to be <100 mg/L and surface tension <60 mN/m) and there are critical methodological deficiencies resulting in the rejection of the study results. Specifically:

- In the absence of analytical method validation report or results of a preliminary solubility experiment there is no evidence that all reasonable efforts have been taken to achieve maximum saturation concentration of the test substance.
- In the absence of a detailed justification as to why analytical detection was not feasible, the lack of analytical monitoring is not justified;
- You did not provide any analytical monitoring of the test concentrations to confirm that the concentration of the test material was maintained within 20 % of the nominal or measured initial concentration throughout the test.

Therefore, the requirements of OECD TG 201 are not met.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained in A.1, the Substance is difficult to test. Therefore, you must fulfil the requirements for difficult to test UVCBs as described in 'Study design' under A.1.

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

1. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

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

While you have not indicated your adaptation, ECHA understands that you have adapted this information requirement by using a weight of evidence approach under Annex XI, Section 1.2.

Your dossier contains the following information:

i. A reproduction/Developmental Toxicity Screening Test (OECD TG 421; [redacted] 2013) conducted with dihydro-3-(tripropenyl)furan-2,5-dione (TSA; EC No. 295-556-6) (key study)
ii. A 14-day dose range finder conducted with the Substance (supporting study)
iii. Information on trimellitic anhydride (CAS 552-30-7) and phthalic anhydride (CAS 85-44-9) from the Concise International Chemical Assessment Document (CICAD) on cyclic acid anhydrides (CICAD, 2009; also attached in the IUCLID Section 13; supporting study)

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the information required for the repeated dose toxicity.

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

As explained under Appendix on 'Reasons common to several requests', Section 1, 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 8.6.1 at Annex VIII 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 including among others haematological (full-scale) and clinical chemistry (full-scale) analysis,
3) organ and tissue toxicity including among others information on terminal observations on organ weights, gross pathology and histopathology (full-scale).

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.

This information is covered by information similar to the OECD TG 407/422.

The sources of information (i) and (ii) provide

- relevant information on the in-life observations;
- some relevant information on the blood chemistry. Source of information (i) informs only on thyroid hormone levels while the source of information (ii) covers limited panel of haematological and clinical chemistry analysis. However, neither of these studies cover all the analyses of haematological and clinical chemistry parameters as expected in OECD TG 407/422;
- some relevant information on the organ and tissue toxicity. The source of information

(i) provides information on the organ and tissue toxicity of reproductive organd and kidneys, but does not cover the full scale of organs as expected in OECD TG 407/422 and no information on the histopathology of organs is provided in study (ii).

The studies referenced in CICAD (2009) review (source of information iii) on cyclic acid anhydride category may provide relevant information on in-life observations, blood chemistry and organ and tissue toxicity.

However, the sources of information have the following deficiencies affecting their reliability:

A. The reliability of the sources of information (i) and (iii) provided with the analogue substances is significantly affected by the deficiency identified and explained under Appendix on 'Reasons common to several requests', Section 1. Particularly, there are issues with applicability domain, characterisation of group members and data density to support predictions within the 'C8-12 Alkenyl Succinic Anhydride Category' and with documentation to support predictions from the 'cyclic acid anhydride' category.

B. In order to be considered compliant the set of information provided has to meet the requirements of OECD TG 407. The criteria of this test guideline include that at least 10 animals (five female and five male) should be used at each dose level.

   The study (ii) that you have provided were conducted with 3 males and 3 females for each dose level. Therefore, the statistical power of the study (ii) provided is limited.

   Therefore, as a result of this limited statisitical power, the weight of this study (ii) is affected and its contribution to a reliable conclusion is limited.

Based on the above, the sources of information (i-iii) do not inform reliably on the in-life observations, blood chemistry, as well as organ and tissue toxicity as foreseen to be investigated in OECD TG 407/422.

Conclusion

Together, the sources of information may provide relevant information on in-life observations, blood chemistry, as well as organ and tissue toxicity as expected in OECD TG 407/422. However, the sources do not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

Therefore, 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 a short-term repeated toxicity study (28-day).

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

Information requested

Column 2 of Annex VIII, Section 8.6.1. provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section C.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

2. 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 in your registration dossier:

i. key study according to OECD TG 203 (2014, [redacted])
ii. a supporting study #1 according to internal lab protocol (1997, [redacted]
iii. a supporting study #2 according to internal lab protocol (1996, [redacted])

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with OECD TG 203 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

- if the test material is tested at the saturation concentration, evidence must be provided that all reasonable efforts have been taken to achieve a saturation concentration, which include: (1) an analytical method validation report demonstrating that the analytical method is appropriate, and (2) the results of a preliminary experiment demonstrating that the test solution preparation method is adequate to maximize the concentration of the test material in solution;
- 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. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided. This justification should confirm that the analytical methods attempted were state of the art, and include a justification as to why detection lower limits were not feasible (any preliminary analytical efforts should also be described in the report);
- the analytical measurement of test concentrations is conducted.
- chemical specific analysis of the test solutions is required to demonstrate stability of exposure concentrations during the test. Only when the concentration of the test material has been maintained within 20% of the nominal or measured initial concentration throughout the test can the results be based on nominal or measured initial concentration.

Your registration dossier provides one key OECD TG 203 test, and two supporting short-term fish toxicity tests using internal lab protocols, showing the following:

- No analytical method validation report or results of a preliminary solubility experiment demonstrating that the test solution preparation method is adequate to maximize the

concentration of the test material in solution are provided in the dossier; in your comments to the draft decision, you indicate your intention to update the robust study summary for key OECD TG 203 study ([redacted] 2014) with further details, including a 96-hour static-renewal range-finding test where 100% mortality was observed at the highest nominal loading, which you indicate equates to a maximum saturation concentration used to select the doses of the definitive test.

- No analytical measurement of test concentrations was conducted in the key OECD TG 203 study ([redacted] 2014) or the supporting studies ([redacted] 1997; [redacted] 1996);
- You state in the robust study summary for the key study that analytical monitoring was not conducted due to the complex/unknown composition and the lack of an analytical reference standard. But you do not provide detailed justification for why the analytical monitoring of exposure concentrations is not technically feasible including information of the methods attempted, confirmation that these were state of the art, or details of the results obtained from these efforts;
- You based the EC50 on nominal concentrations, but you did not demonstrate that concentration of the test material was maintained within 20% of the nominal or measured initial concentration throughout the test.

The Substance is difficult to test (based on OECD GD 23 indicator values of Log Kow >4, saturation concentration in aqueous media expected to be <100 mg/L and surface tension <60 mN/m) and there are critical methodological deficiencies resulting in the rejection of the study results. Specifically:

- In the absence of analytical method validation report or results of a preliminary solubility experiment there is no evidence that all reasonable efforts have been taken to achieve maximum saturation concentration of the test substance. Information on the range-finding test, which you mention in your comments to the draft decision, is already available in your registration dossier. Contrary to your comments, the range-finding test does not provide evidence that the maximum saturation concentration of the test substance was achieved in the definitive test due to the following reasons. First, in the absence of analytical determination of exposure concentrations in the range-finding test, you have not demonstrated that maximum saturated concentration was achieved. Second, there are some differences in the preparation of test solutions in the range-finding test and in the definitive test: after direct addition of test material and 20-h stirring, test solutions were allowed to settle for 1h in the range-finding test and for 4h in the definitive test before being siphoned off. This difference might have led to differences in the actual exposure concentrations, since at the same nominal loading (100 mg TPSA/L), 100% mortality was observed in the range-finding test while no mortality was observed in the definitive test.
- In the absence of a detailed justification as to why analytical detection was not feasible, the lack of analytical monitoring is not justified.
- You did not provide any analytical monitoring of the test concentrations to confirm that the concentration of the test material was maintained within 20 % of the nominal or measured initial concentration throughout the test.

Therefore, the requirements of OECD TG 203 are not met.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

To support the proposed adaptation for this endpoint, you indicate your intention to update the robust study summary for key OECD TG 203 study ([redacted], 2014), which you consider

to be valuable to elucidate the aquatic toxicity of the Substance. However, as explained above, based on the available information this study with the Substance does not meet the requirements of OECD TG 203 therefore it cannot be used as supporting information.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

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.

3. **Simulation testing on ultimate degradation in surface water; and**
4. **Soil simulation testing; and**
5. **Sediment simulation testing**

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP), when:
  - it is not readily biodegradable (*i.e.* <60% degradation in OECD 301D/F)
  - it is not readily biodegradable based on (Q)SAR model if the criteria specified under Section 1.3 of Annex XI are met. The Biowin model provides an overall conclusion on ready biodegradation only if Biowin3 (ultimate survey model) result is "weeks" or faster (e.g. days or days to weeks) ≥2.75 AND Biowin5 (MITI linear model) ≥0.5 (ECHA Guidance R.7.9.4.1).
  - the degradation half-life is >60 days in marine waters, or >40 days in fresh or estuarine water, or >180 days in marine sediments, or >120 days in fresh or estuarine water sediments, or soils (in this case the Substance is considered P). (Annex XIII, Section 1.1.1)
  - the degradation half-life in surface waters is >60 days or >180 days in sediments/soils (in this case the Substance is considered vP). (Annex XIII, Section 1.2.1).
- it is potentially bioaccumulative or very bioaccumulative (B/vB), when:
  - it has a high potential to partition to lipid storage (*e.g.* log K_{ow} > 4.5);
  - for some groups of substances (e.g. ionisable substances, surfactants) mechanisms other than lipid partitioning may drive bioaccumulation (e.g. binding to protein/cell membranes).

When using results from QSAR models to screen the potential PBT/vPvB properties the following conditions under Annex XI, Section 1.3. must be fulfilled:

- the prediction needs to be derived from a scientifically valid model,

- the substance must fall within the applicability domain of the model,
- results need to be adequate for the purpose of risk assessment or classification and labelling, and
- adequate and reliable documentation of the method must be provided.

Your registration dossier provides the following:

- Two OECD 301 series tests indicating that the Substance is not readily biodegradable i.e. 9.9% degradation after 28 days in OECD TG 301D, and 0% degradation after 28 days in OECD TG 301F;
- The following results from the BIOWIN QSAR for the Substance: '*The BIOWIN model shows that although the substance was predicted to be not readily biodegradable, ultimate biodegradation was predicted to occur in the timeframe of weeks.*' No documentation supporting the use of this QSAR (QMRF and QPRF) is provided;
- The Substance has a high potential to partition to lipid storage (Log K_{ow} of >4.38 based on OECD TG 107);
- The Substance is ionisable and surface active (surface tension provided in the dossier: 28.6 nM/m).

In your PBT assessment, you have concluded that *"the substance may be described as potentially "persistent" ("P") and potentially "very persistent" ("vP"), based on the screening criteria for ready biodegradability, although the results of hydrolysis testing and the predictions of the BIOWIN 3 module for the hydrolysis product indicate that the substance is unlikely to be very persistent in the environment"*.

On the basis of this information we conclude the following:

1. The substance is not readily biodegradable and hence is potentially P/vP;
2. The reported Log Kow is >4.38 and therefore it cannot be excluded that the Log Kow would not exceed the screening threshold of 4.5. However, the Substance is ionisable and surface active. Therefore, high potential for bioaccumulation cannot be excluded based on available information. You have provided no information that considers mechanisms of uptake due to the ionisable and surface-active properties of the Substance. Based on these ionisable and surface-active properties the Substance is considered potentially bioaccumulative.

Your conclusion of non-vP is based on BIOWIN predictions. In the absence of details on the model and the predictions, we cannot assess the information provided. Furthermore, the prediction from Biowin 3 alone cannot be used to conclude that the Substance or its hydrolysis products would not be persistent or very persistent. A conclusion on P/vP requires data on the Substance half-life in surface waters or sediments/soils (Annex XIII Section 1) as described above. You do not provide degradation half-life data in your dossier for surface waters, soils or sediments. In contrast, the provided OECD TG 301D and 301F studies already indicate that the Substance is potentially persistent.

As explained above, the information above indicates that the Substance is a potential PBT/vPvB substance. The Substance has low water solubility (10-20 mg/L), high partition coefficient (Log Kow>4.38) and is surface active and ionisable, indicating high potential to adsorb to soil and sediment.

Based on the adsorptive properties of the substance, soil and sediment represent relevant environmental compartments. The results of the submitted adsorption study (Study entitled: 'TPSA – Determining the Adsorption Coefficient (Koc) Following OECD Guideline 106', 2012)

cannot be used to indicate low potential for adsorption for the reasons described below in the examination of the information provided in Appendices C.6 to C.7.

Surface water is a relevant compartment based on available water solubility data (water solubility > 1µg/L) and the potential for releases to the aquatic compartment (e.g. note ERC2: Formulation into mixture).

Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation. Simulation tests on ultimate degradation in surface water (OECD TG 309), soil (OECD TG 307), and sediment (OECD TG 308) are therefore required.

The examination of the available information or adaptations, as well as the selection of the requested tests and the test designs are addressed respectively in Appendices C.5 to C.7.

6. Identification of degradation products

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As already explained under Section B.3 to B.5, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

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

You have not addressed the potential formation of stable degradation products with PBT/vPvB properties.

Therefore, this information requirement is not met.

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

On this basis, the information requirement is not fulfilled. The identification of degradation products is therefore required.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed respectively in Appendices C.5 to C.8.

7. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as:

  - is not readily biodegradable (i.e. <60/70% degradation in an OECD TG 301 series test), and;
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
  - it has a high potential to partition to lipid storage (*e.g.* log K_{ow} > 4.5);
  - for some groups of substances (e.g. ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid.

Your registration dossier provides the following:

- The results of two OECD TG 301 series tests for ready biodegradability. The Substance is not readily biodegradable in the key study (9.9% degradation after 28 days in OECD TG 301D); or the supporting study (0% degradation after 28 days in OECD TG 301F);
- The Substance has a high potential to partition to lipid storage (Log K_{ow} of >4.38 based on OECD TG 107);
- The Substance is a surfactant (surface tension provided in the dossier: 28.6 mN/m) and ionisable, and therefore high potential for bioaccumulation cannot be excluded based on available information.

In your PBT assessment, you have concluded that the Substance is not B or vB based on (1) a partition coefficient that does not clearly indicate that the Substance would meet the screening criterion log Kow ≤ 4.5, and (2) the rapid hydrolysis of the Substance and the assumption that hydrolysis products are more hydrophilic and as a consequence will have a lower potential for bioaccumulation.

We have assessed the provided information and conclude the following:

- The Substance is not readily biodegradable and hence is potentially P/vP;
- The reported logKow is >4.38 and therefore it cannot be excluded that the logKow would not exceed the screening threshold of 4.5. However, the Substance is ionisable and surface active. Therefore, high potential for bioaccumulation cannot be excluded based on available information. You have provided no consideration of mechanisms of uptake due to the ionisable and surface active properties of the Substance.
- Your conclusion on B is based on the fact that the Substance rapidly hydrolyses. As abiotic degradation is primary degradation, careful consideration needs to be given to the potential formation of stable degradation products with PBT/vPvB properties. You have not addressed the potential formation of stable degradation products and their related PBT/vPvB properties.

Furthermore, the information in your dossier is currently incomplete and therefore:
- it is not possible to conclude on the persistence of the Substance (see Appendices B.3 to B.6 of this decision), and
- it is not possible to conclude on the toxicity of the Substance (see Appendices A.1 to A.2; B.2 to B.2; C.1 to C.4; and D.1).

The information above indicates that the Substance is a potential PBT/vPvB substance.

Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Appendix C.9.

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 this information requirement by using an Annex IX, Section 8.6.2, Column 2 adaptation. You state that "*According to Regulation (EC) No.1907/2006, Annex IX, 8.6.2, Column 2, a sub-chronic toxicity study (90-days) does not need to be conducted if a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake). The substance has been documented to be unstable in aqueous buffers, with a half-life of minutes at a temperature of 35 degrees C (Hydrolysis, Section 5.1.2). It is not known whether a full data set exists for the cleavage product [butanedioic acid, (tetrapropenyl]. [….]The current OECD 421 study of oral administration of the anhyride (performed according to GLP) identifies a NOAEL for repeated dose effects, which are most likely due to exposure to the cleavage product. [….] While data are limited, the UNEP, in its review of cyclic acid anhydrides (CICAD, 2009) did not identify repeated dose toxicity as a major critical effect of exposure*."

To support the adaptation, you have provided following information:

i. A Reproduction/Developmental Toxicity Screening Test (OECD TG 421; [redacted] 2013) conducted with dihydro-3-(tripropenyl)furan-2,5-dione (TSA; EC No. 295-556-6), key study
ii. Information on the Concise International Chemical Assessment Document (CICAD) on cyclic acid anhydrides (CICAD, 2009; attached in the IUCLID Section 13), supporting study
iii. A Hydrolysis as a Function of pH study (OECD TG 111) for the Substance ([redacted], 2013; under Hydrolysis in IUCLID section 5.1.2), key study

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

As provided in Annex IX, Section 8.6.2, Column 2, third indent, you may adapt the information requirement, provided that

- the Substance undergoes immediate disintegration and
- there are sufficient data on the cleavage products

You have provided a hydrolysis study (OECD TG 111) for the Substance (iii). Based on this, you consider that "*The substance has been documented to be unstable in aqueous buffers*".

Regarding the second criterion, you did not provide data on the cleavage product. In fact, you state that "*It is not known whether a full data set exists for the cleavage product [butanedioic acid, (tetrapropenyl].*". You further mention that "*The current OECD 421 study of oral administration of the anhydride* [analogue substance 4, TSA] *(performed according to GLP) identifies a NOAEL for repeated dose effects, which are most likely due to exposure to the cleavage product*." and refer to the refer to the review of cyclic acid anhydrides (CICAD, 2009) and indicate that in this review, the repeated dose toxicity was not identified as a major critical effect.

The OECD TG 111 hydrolysis study indicates that 50% of the Substance is hydrolysed (DT50) in 17 minutes at pH 4 (35°C), while it takes 55 minutes to reach 90% level of hydrolysis at the same conditions. On the other hand, at pH 7 (35°C), the DT50 for the Substance is 9.2 minutes and DT90 is 31 minutes. This indicates that the hydrolysis rate is reduced with the reduced pH and therefore, would be further reduced at the lower than pH 4 present in the

stomach following oral exposure. Therefore, you have not demonstrated that the Substance would undergo immediate disintegration under physiological conditions.

You have not provided any information on the proposed cleavage product butanedioic acid, (tetrapropenyl).

For the information provided on the analogue substances (i-ii), ECHA refers to the deficiencies identified in the category approach as explained under Appendix on 'Reasons common to several requests', Section 1. As you have not established that relevant properties of the Substance can be predicted from data on the analogue substances, the information on the analogue substances do not inform on the the properties of the cleavage product of the substance either.

As you have not demonstrated that the Substance undergoes immediate disintegration or provided information on the cleavage products; therefore, your adaptation under the Annex IX, section 8.6.2, column 2 is rejected, and the information provided does not fulfil the information requirement.

Information on the design of the study to be performed (species/route)

Following 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[15]. The study should be performed with oral administration because the Substance is a liquid of low vapour pressure (76.5 Pa at 20°C) and no uses with spray applications are reported, that could potentially lead to aerosols of inhalable size.

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

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

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 provided following information:

i. A Reproduction/Developmental Toxicity Screening Test (OECD TG 421; [redacted] 2013) conducted with dihydro-3-(tripropenyl)furan-2,5-dione (TSA from category 'C8-12 Alkenyl Succinic Anhydride Category'; EC No. 295-556-6)
ii. Information on trimellitic anhydride (CAS 552-30-7), phthalic anhydride (CAS No. CAS 85-44-9), succinic anhydride (CAS 108-30-5) and maleic anhydride (CAS 108-31-6) from the Concise International Chemical Assessment Document (CICAD) on cyclic acid anhydrides (CICAD, 2009; also attached in the IUCLID Section 13; supporting study)

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

iii. Hydrolysis as a Function of pH study (OECD TG 111) for the Substance ([redacted] 2013; under Hydrolysis in IUCLID section 5.1.2)

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

You did neither provide the standard information nor an indication of a particular specific or general adaptation according the REACH Regulation.

As you may have intended to submit the information as an adaptation of the standard information either under Annex XI, section 2 or under Annex XI, Section 1.2, ECHA highlights the following shortcomings leading to the rejection of the adaptation.

Annex XI, section 2 adaptation

You state that "*The conduct of a developmental toxicity study (OECD 414) is not technically feasible on the registered substance, the alkenyl succinic anhydride. The substance has been documented to be unstable in aqueous buffers, with a half-life of minutes at a temperature of 35 degrees C (Hydrolysis, Section 5.1.2). The effects of oral administration of the substance cannot be studied in mammalian systems. The break-down product [butanedioic acid, (tetrapropenyl)-] may be studied, but prior to proposing to undertake a study using animals, it is critical to assess whether the data is available from the registrants of this substance. While data are limited, the UNEP, in its review of cyclic acid anhydrides (CICAD, 2009) did not identify reproductive toxicity or repeated dose toxicity as a major critical effect of exposure*."

As explained in the Appendix on 'Reasons common to several requests', Section 2, your adaptation in accordance with Annex XI, Section 2 is rejected. Particularly, you have not provided any considerations for testing via dietary route or using another vehicle.

Therefore, the information provided does not fulfil the information requirement.

Annex XI, section 1.2 weight of evidence adaptation

Based on the presented sources of information (source i-ii above), you argue that the available data gives sufficient information to conclude on the information required for the pre-natal developmental toxicity.

As explained under Appendix on 'Reasons common to several requests', Section 1, 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 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.

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).

The source of information (i) provide some relevant information on the prenatal developmental toxicity. However, the source of information do not investigate structural malformations and variations (external, visceral and skeletal) as expected in OECD TG 414.

The studies referenced in CICAD (2009) review (source of information ii) on cyclic acid anhydride category may provide relevant information on pre-natal developmental toxicity.

However, the sources of information have the following deficiencies affecting their reliability:

A. The reliability of the sources of information (i) and (ii) provided with the analogue substances is significantly affected by the deficiency identified and explained under Appendix on 'Reasons common to several requests', Section 1. Particularly, there are issues with applicability domain, characterisation of group members and data density to support predictions within the 'C8-12 Alkenyl Succinic Anhydride Category' and with documentation to support predictions from the 'cyclic acid anhydride' category.

B. In order to be considered compliant the set of information provided has to meet the requirements of OECD TG 414. The criteria of this test guideline include that at least 20 female animals with implantation sites should be used for each test and control group should be used at each dose level.

   The study (i) that you have provided were conducted with 10 females for each test group. Therefore, the statistical power of the study (i) provided is limited.

   Therefore, as a result of this limited statisitical power, the weight of this study (i) is affected and its contribution to a reliable conclusion is limited.

Based on the above, the sources of information (i-ii) do not inform reliably on the prenatal developmental toxicity as foreseen to be investigated in OECD TG 414.

Maternal toxicity and maintenance of pregnancy

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams while the maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

The studies referenced in CICAD (2009) review (source of information ii) on cyclic acid anhydride category may provide relevant information on on the maternal toxicity and maintenance of pregnancy.

The source of information (i) provide relevant information on the maternal toxicity and maintenance of pregnancy.

However, the reliability of the sources of information is affected by the issues identified in the use of information from the structurally related substances (sources i and ii) as well as in the insufficient number of animals tested, not meeting the requirements of OECD TG 414 (i) as already explained in the section on "prenatal developmental toxicity" above.

Based on above, the sources of information (i-ii) do not inform reliably on the maternal toxicity and maintenance of pregnancy as foreseen to be investigated in OECD TG 414.

Conclusion

Together, the sources of information may provide relevant information on developmental toxicity, maternal toxicity and maintenance of pregnancy as expected in OECD TG 414. However, the sources do not reliably contribute to a weight of evidence intended to identify the properties of the Substance.

Therefore, 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.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Information on study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[16] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates

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

You have provided the following information in your registration dossier:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: '*According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, long-term aquatic toxicity testing shall be conducted if the substance is poorly soluble in water, or if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. The substance is soluble in water, and the chemical safety assessment indicated that aquatic exposures do not require further investigation; the risk characterisation ratios for surface water are below one. Therefore, in accordance with Annex I, the risks are considered to be controlled, and long-term toxicity testing of aquatic invertebrates is not indicated*.'

We have assessed this information and identified the following issues:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section

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

1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Study design

To fulfil the information requirement for long-term toxicity testing on invertebrates, the Daphnia magna Reproduction Test (test method OECD TG 211) is the most appropriate (ECHA Guidance R.7.8.4.).

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

4. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided the following information in your registration dossier:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: '*According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, long-term aquatic toxicity testing shall be conducted if the substance is poorly soluble in water, or if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. The substance is soluble in water, and the chemical safety assessment indicated that aquatic exposures do not require further investigation; the risk characterisation ratios for surface water are below one. Therefore, in accordance with Annex I, the risks are considered to be controlled, and long-term toxicity testing of fish is not indicated*.'

We have assessed this information and identified the following issues:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

In the comments to the draft decision, you state further that: "*we will further investigate the applicability of the aquatic toxicity data already generated for TPS acid, as well as further details from a short-term fish toxicity study using TPSA to provide sufficient justification to fulfil this endpoint requirement, also in consideration of an updated Chemical Safety Assessment (CSA)".* However, as explained above Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity testing to fish under Column 1 referring to the Chemical Safety Assessment.

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 in A.1, the Substance is difficult to test. Therefore, you must fulfil the requirements for difficult to test UVCBs as described in 'Study design' under A.1.

5. Simulation testing on ultimate degradation in surface water

Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.) for substances with water solubility > 1µg/L.

The Substance has a water solubility of 10-20 mg/L. Hence the degradation testing in the surface water compartment is relevant for the Substance.

Your registration dossier provides the following:

An adaptation under Annex IX, Section 9.2., Column 2 with the following justification:

'According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, further biodegradation testing, including testing for ultimate biodegradation in surface water…..shall be proposed if the chemical safety assessment according to Annex 1 indicates the need to investigate further the degradation of the substance or its degradation products; additional testing need not be proposed if direct and indirect exposure to the relevant environmental compartment is unlikely. The chemical safety assessment did not indicate the need to investigate the degradation of the substance; the risk characterisation ratios for surface water are below one. Therefore, in accordance with Annex I, the risks are considered to be controlled. Therefore, simulation testing in surface water is not indicated.'

We have assessed this information and identified the following issues:

1. Under Section 9.2., Column 2 of Annex IX to REACH, the study may be omitted if the chemical safety assessment (CSA) does not indicate the need for further biotic degradation testing. The CSA does indicate such need (Annex I, Section 4; Annex XIII, Section 2.1) if, for instance, the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4). This is the case if the Substance itself or any of its constituent, impurity or transformation/degradation product present in concentration ≥ 0.1% (w/w) meets the criteria already listed in Appendix B.3 to B.6.

Your adaptations for these information requirements are based on chemical safety assessment: "*the risks are considered to be controlled*".

As already explained under Appendix B3 to B6, the CSA indicates the need for further biotic degradation testing and your adaption is therefore rejected.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made. You remain responsible for complying with this decision by the set deadline.

A test conducted according to OECD TG 309 would fulfil the information requirement (refer to Study Design below).

6. **Soil simulation testing; and**
7. **Sediment simulation testing**

Soil simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.3.) for substances with a high potential for adsorption to soil

Sediment simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.4.) for substances with a high potential for adsorption to sediments.

Your registration dossier provides the following justification to omit testing: You state that*: 'The experimentally-determined Koc for the substance is 825; this value falls within the range of Koc values of 500-1000, below which substances are unlikely to adsorb to sediment or soil. The chemical safety assessment did not indicate the need to investigate the degradation of the substance; the risk characterisation ratios for sediment and soil are below one. Therefore, in accordance with Annex I, the risks are considered to be controlled. Therefore, simulation testing in sediment or soil is not indicated.'*

Your statements relate to two possible ways of omitting the required standard information, but ECHA has identified issues with both of these on the basis of the information that you provided.

First, under Section 9.2., Column 2 of Annex IX to REACH, the study may be omitted if the chemical safety assessment (CSA) does not indicate the need for further biotic degradation testing. The CSA does indicate such need (Annex I, Section 4; Annex XIII, Section 2.1) if, for instance, the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4). This is the case if the Substance itself or any of its constituent, impurity or transformation/degradation product present in concentration ≥ 0.1% (w/w) meets the criteria already listed in Appendix B.3 to B.6"

As already explained under Appendix B3 to B6, the CSA indicates the need for further biotic degradation testing and your adaption is therefore rejected.

Second, soil and sediment simulation testing is required for substances with a high potential for adsorption (Section 9.2.1.3 and Section 9.2.1.4 of Annex IX).

You state that the Substance has low potential for adsorption.

We note that that the Substance has relatively low water solubility (10-20 mg/L) and is surface active and ionisable.

For soil and sediment simulation you also refer to experimentally derived Log Koc and state that the substance is unlikely to adsorb to sediment. This study according to OECD TG 106 indicates that the Koc is 825. This test used activated sludge at sorbent (dry weight) to solution ratios of 1:100, 1:200 and 1:400, a pH range 5.37-5.62, and no chemical specific analytical measurements for the concentration of the test substance were performed.

1. You indicate that further degradation testing in sediments and soil should be waived based on the Koc measurement from the submitted OECD TG 106. We have assessed the information provided and found the following deficiencies:

- OECD TG 106 is applicable to chemical substances for which an analytical method with sufficient accuracy is available. You did not use a chemical specific analytical method.
- OECD TG 106 recommends the use of multiple soil types, and testing with soils with varying pHs for ionisable substances as stated in the TG: '*For ionisable test substances, the selected soils should cover a wide range of pH, in order to evaluate the adsorption of the substance in its ionised and unionised forms*.' You used a single sample of activated sludge and a pH range of minimal variation (pH 5.37-5.62).
- The recommended soil/solution ratios in OECD TG 106 are 1:1, 1:5 and 1:25 (although these can go as high as 1:100 for substances with very high Kd). The sludge (sorbent) to solution ratios used in the provided test were 1:100, 1:200 and 1:400. These are inconsistent with TG 106 and are dilution rates much higher than recommended.
- ECHA Guidance R7a states that 'for ionisable substances, partition coefficients should be corrected according to the pH of the environment being assessed. For complex mixtures (e.g. UVCBs), a single value of *K*oc will not be definitive. In such cases a range of values or a representative value can be given, depending on the substance.' You have not investigated the influence of pH on adsorption, nor have you provided a range of values for different components of the UVCB.
- The Koc results provided are therefore incompliant with OECD TG 106 and cannot be considered to be reliable.

2. The substance is surface active and ionisable and therefore has high potential for adsorption to soil and sediment. Ionisable and surface active substances 'can bind to substrates of opposite charge e.g. cationically charged substances bind to negatively charged humic acids, clay, microorganisms etc; anionic compounds bind to positively charged Si, Al or Fe oxide', and exhibit 'high adsorption or binding behaviour that is not driven by lipophilicity.' (ECHA Guidance R7.b, p.73 and p.156). Simulation testing for sediments and soils is therefore relevant to this Substance.

As assessed above, the information requirement for simulation testing of ultimate degradation in soils and sediments is required, and is not currently fulfilled. Tests conducted according to OECD TG 307 and OECD TG 308 would fulfil these information requirements.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made. You remain responsible for complying with this decision by the set deadline.

Study designs for the Simulation tests

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):
1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 307-309.

Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 307-309; ECHA Guidance R.11.4.1.).

In accordance with the specifications of OECD TG 307-309, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Further details on the study designs are provided below for simulation tests on ultimate degradation in surface water (OECD TG 309), soil (OECD TG 307), and sediment (OECD TG 308), respectively.

Surface water (OECD TG 309):

You must perform the OECD TG 309 test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (ECHA Guidance R.11.4.1.1.3.).

As specified in ECHA Guidance R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test substance concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified as specified above.

Soil Simulation Study (OECD TG 307)

In accordance with the specifications of OECD TG 307, you must perform the test using at least four soils representing a range of relevant soils (*i.e.* varying in their organic content, pH, clay content and microbial biomass).

Sediment Simulation Study (OECD TG 308)

In accordance with the specifications of OECD TG 308, you must perform the test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture. If the Substance may also reach marine waters, at least one of the water-sediment systems should be of marine origin.

8. Identification of degradation products

Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

You have provided the following information:

i. an adaptation under Annex IX, Section 9.2., Column 2 as described above (see Appendices C.5 to C.7).

We have assessed this information and identified the following issue:

You have not addressed the potential formation of stable degradation products with PBT/vPvB properties.

As already explained under Appendices C.5 to C.7, the CSA indicates the need for further biotic degradation testing and your adaption is therefore rejected.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Study Design

Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation studies requested under C.5 to C.7 or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Appendix C.5) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, *e.g.* 20°C) and at higher application rate (*i.e.* > 100 µg/L).

To determine the degradation rate of the Substance, the requested studies according to OECD TG 308/307 (Appendices C.6 and C.7) must be conducted at 12°C and at a test material application rate reflecting realistic assumptions. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline) and at higher application rate (*e.g.* 10 times).

9. Bioaccumulation in aquatic species

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

You have provided the following information:

- An adaptation under Annex IX, Section 9.3.2., Column 2 with the following justification: '*Testing for bioaccumulation in aquatic species was waived. The substance undergoes rapid hydrolysis at environmentally relevant temperatures and*

pH conditions, with experimentally-determined half-life values substantially below the threshold half-life of 12 hours, below which it may be assumed that the rate of hydrolysis is greater than that for uptake by exposed organisms. Therefore, the substance has a low potential for bioaccumulation, and direct or indirect exposure of the aquatic compartment is unlikely, in accordance with Regulation (EC) No.1907/2006, Annex IX, Column 2. Therefore, bioaccumulation testing of the substance in aquatic species is not indicated.'

We have assessed this information and identified the following issues:

- Column 2 of Annex IX to REACH states that a study is not necessary if direct and indirect exposure of the aquatic compartment is unlikely. This implies that there is a low probability of – rather than low extent of – exposure and opportunities for exposure-based waiving will therefore be limited (ECHA Guidance R.7.10.4.5);
- Furthermore, as stated in ECHA Guidance R.7.10.4.5, exposure considerations to adapt this information requirement must take into account assessment of PBT/vPvB properties according to Annex XIII;
- under Annex XIII section 2.1 (ECHA Guidance R.11) the possibility to refrain from testing (or generating other necessary information) to conclude on PBT/vPvB is only an option when the substance is treated "as if it is a PBT or vPvB" and the process and use conditions of the substance meet strictly controlled conditions as specified in Section 3.2(b) or (c) of Annex XI;
- Annex XIII (5th paragraph) requires that the PBT/vPvB properties of degradation products are assessed. In addition, where the hydrolysis half-life, at environmentally relevant pH values (4-9) and temperature, is less than 12 hours, ECHA Guidance (R.7.10.3.4) indicates the need to assess the hazards, including bioaccumulation potential, of relevant hydrolysis products (ECHA Guidance R.7.10.3.4).

Your waiver is based on the fact that the Substance rapidly hydrolyses and that exposure of the aquatic environment is unlikely.

You have provided a hydrolysis study (OECD TG 111; [redacted], 2013) with the Substance that indicates it is rapidly hydrolysed at pH 4, 7 and 9 at temperatures of 15, 25 and 35 ºC. For example, at pH 7 the calculated half-life (DT50) was 44 minutes at 15 ºC, and 22 minutes at 25 ºC.

The Substance is used as an epoxy curing agent, and as an intermediate in the production of lubricants. Product categories formulated with the Substance include: (1) Coatings and paints, thinners, paint removers (PC9a), and (2) Polymer preparations and compounds (PC32). The environmental release category identified for this Substance is ERC2: Formulation into mixture.

As explained under sections B.3 to B.7, the PBT assessment of the Substance is not yet complete. Based on the uses of the Substance, the Substance can be expected to be released to the aquatic environment and you have not indicated that strictly controlled conditions would apply. Therefore, your arguments to refrain from testing based on exposure considerations are not accepted.

As abiotic degradation is only primary degradation, careful consideration needs to be given to the potential formation of stable degradation products with PBT/vPvB properties. You have not addressed the potential formation of stable degradation products with PBT/vPvB properties.

Instead of adapting this information requirement based on rapid hydrolysis, you need to consider performing an exposure assessment, a hazard assessment and a bioaccumulation

test on the relevant hydrolysis products instead of the parent substance.

In your comments to the draft decision, you indicate your intention to adapt this information requirement by means of grouping and read-across approach according to Annex XI, Section 1.5, of the REACH Regulation.

As explained under Appendix on 'Reasons common to several requests', Section 1, no conclusion on the compliance of the proposed adaptation can currently be made.

On this basis, the information requirement is not fulfilled. You remain responsible for complying with this decision by the set deadline.

Study design

Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (ECHA Guidance R.7.10.3.1.).

Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:
· a stable and fully dissolved concentration of the test substance in water cannot be maintained within ± 20% of the mean measured value, and/or
· the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

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

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

Appendix D: Reasons to request information required under Annex X of REACH

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

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

While you have not indicated the adaptation, ECHA understands that you have adapted this information requirement by using an Annex XI, Section 2 adaptation.

You state that "*The conduct of a developmental toxicity study (OECD 414) is not technically feasible on the registered substance, the alkenyl succinic anhydride. The substance has been documented to be unstable in aqueous buffers, with a half-life of minutes at a temperature of 35 degrees C (Hydrolysis, Section 5.1.2). The effects of oral administration of the substance cannot be studied in mammalian systems. The break-down product [butanedioic acid, (tetrapropenyl)-] may be studied, but prior to proposing to undertake a study using animals, it is critical to assess whether the data is available from the registrants of this substance. While data are limited, the UNEP, in its review of cyclic acid anhydrides (CICAD, 2009) did not identify reproductive toxicity or repeated dose toxicity as a major critical effect of exposure*."

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

As explained in the Appendix on 'Reasons common to several requests', Section 2, your adaptation in accordance with Annex XI, Section 2 is rejected. Particularly, you have not provided any considerations for testing via dietary route or using another vehicle.

Therefore, the information provided does not fulfil the information requirement.

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

You also propose to conduct dose range finding study with the rabbit to determine whether rabbit is suitable species for testing. ECHA notes that the rat or rabbit are the preferred second species tested depending on the species tested in the first PNDT study. If a species other than the rat and the rabbit is selected as the first or second species, the selection should be justified.[15] In addition, you propose to generate toxicokinetic (hydrolysis) information in rat and rabbit to support your new read-across approach discussed under the Appendix on Reasons common to several requests, section 3. The generation of information to support the proposed adaptation is at your discretion.

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request Appendix C, request 2 in this decision).

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[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:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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

a) 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.
b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm 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 F: General recommendations when conducting and reporting new tests for REACH purposes

A. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

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

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

B. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (Section R.11.4.2.2), you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

Appendix G: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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

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

The compliance check was initiated on 28 August 2020.

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

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

Deadline to submit the requested information in this decision

You requested an extension of the deadline for the Sub-chronic toxicity study (90-day) from 12 months specified in the decision to 42 months. You argue that the extension is needed to generate sufficient read-across data to justify the preliminary read-across strategy.

As indicated above, the deadline set in the decision allows for the development of the appropriate studies for fulfilling the standard information requirements addressed in the decision. As indicated in the Appendix on Reasons common to several requests above, you stated your intention to fulfil the information requirements under consideration by other means than by generating the requested information.

The timeline set in this decision allows for generating the required data on the Substance as a result of incompliances identified in the dossier submission identified in the header of the document. The objective of this compliance check is for you to fulfil the standard information requirements by the set deadline. Therefore, a further extension of the deadline set in the decision to accommodate your statement of intention to provide an adaptation is considered unjustified.

On this basis, ECHA has not modified the deadline.

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 H: List of references - ECHA Guidance[19] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[20]

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

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

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

OECD Guidance documents[22]

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

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

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

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

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

Appendix I: Addressees of this decision and their corresponding information requirements

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

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

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.