~~Confidential~~

Helsinki, 16 November 2021

Addressees
Registrant(s) of OSA_C8-ASA_JS as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
23/07/2020

Registered substance subject to this decision ("the Substance")
Substance name: 3-(oct-2-en-1-yl)dihydrofuran-2,5-dione
EC number: 629-679-7
CAS number: 42482-06-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***21 February 2024***.

Requested informatpaion 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; Annex VIII, Section 8.6.1.) based on the results of the 'Sub-chronic toxicity study (90 days)', unless a study according to OECD TG 422 is provided for the 'Screening for reproductive/developmental toxicity' requested below

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

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

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

1. 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)

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

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

Information required depends on your tonnage band

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

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

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

How to comply with your information requirements

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

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". 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".

Appeal

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

Failure to comply

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

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

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

Appendix on Reasons common to several requests

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

You seek to adapt the following standard information requirements by grouping substances in a category and applying a read-across approach in accordance with Annex XI, Section 1.5:

- Short-term toxicity testing on 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)

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.

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[2,3].

A. Scope of the grouping

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);
[2] OSA 3-oct-2-en-1-yl dihydrofuran-2,5-dione (EC No. 629-679-7), referred to as "the Substance" thereafter;
[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

"*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.".

[2] 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)
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 Available online: https://doi.org/10.2823/794394

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

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".*[4] 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*".[5] 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.

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 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.

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

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).[6] 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.[7]

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 multiconstituent substances and two are UVCBs (TPSA [1] and TSA [4]).

While the detailed description of the multiconstituent group members are provided, you state for the UVCBs that: '*The main components of TPSA are the [redacted], which is itself a UVCB. [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.

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

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*"[8]. The set of supporting

[6] ECHA Guidance R.6: Section R.6.2.3.1
[7] ECHA Guidance R.6: Section R.6.2.5.5
[8] ECHA Guidance R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on 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:

- 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 water solubility and Log Kow for three of the group members.

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 structures 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.

Adequacy and reliability of source studies

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

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

Specific reasons why your source studies do not meet these criteria are explained further below under the relevant information requirement sections A.2 and B.3.

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.

2. 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- 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 repeated dose toxicity, you have indicated that "*Repeated dose toxicity effects were observed at 150 mg/kg bw/day after 28-days of oral exposure to a chemical category member, tripropenyl succinic anhydride (TSA). The NOAEL is 50 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 toxicity represents a health 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 tripropenyl succinic 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 summaries 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 reliable, 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[9].

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

In your registration dossier you have formed a group (category) called the 'C8-12 Alkenyl Succinic Anhydride' category as previously described above under the Appendix on Reasons common to several requests, Section 1 (approach under Annex XI, Section 1.5). ECHA's assessment of your grouping approach has already been provided above under the Section 1.A (approach under Annex XI, Section 1.5, A. Scope of grouping) and the conclusions also apply to the information requirements listed above under the Section 2 (approach under Annex XI, Section 1.2).

I.2 Predictions for toxicological properties

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

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.

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

The Appendix on Reasons common to several requests, Section 1.B (approach under Annex XI, Section 1.5, B. Prediction of toxicological properties), identifies a deficiency in the characterisation of the group members of the 'C8-12 Alkenyl Succinic Anhydride' category. This finding applies equally to the sources of information relating to analogue substances submitted under your weight of evidence approach.

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.[10] 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 one 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

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

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 one substance in the category, which is not sufficient to establish a trend across the category. In addition, information is only available for the branched alkenyl substituted category members and no repeated dose or reproductive toxicity data has been provided for any of the category members with linear alkene substitution. Without information on the linear alkenyl members of the category, it cannot be concluded that the substances in the category, including the Substance, would have the same type of effects with an identified trend within the group.

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.

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).[11]

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

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.

III. Conclusion on the reliability of the information on analogue substances

Therefore, 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 in the following Appendices.

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

1. Short-term toxicity testing on aquatic invertebrates

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

You have provided the following information:

- OECD TG 202 ([redacted], 2013) key study with TSA[4] using a read across approach.

We have assessed this information and identified the following issue[s]:

As detailed in Appendix 'Reasons common to several requests', Section 1, the read across approach is rejected. On this basis, the information requirement is not fulfilled.

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

Study design

The Substance is difficult to test due to the relatively low water solubility (20 mg/L) and rapid hydrolysis (e.g. half-life of 4 mins at pH 7, 25°C). Note that the indicator values for difficult to test substances in OECD GD 23 include: (1) water solubility of <100 mg/L and, (2) hydrolysis half-life of <24 hours at 25°C within a pH range of 5-9. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

Given the rapid hydrolysis of the substance, ECHA encourages you to consider OECD GD 23 recommendations regarding the identification and quantification of degradation products in order to facilitate interpretation of test results for substances that degrade in the test system. As stated in OECD GD 23, substances may transform (via hydrolysis) to substances of higher concern. It is therefore important to consider the aquatic toxicity of the hydrolysis products in the test design.

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:

- OECD TG 201 study with TPSA[1] ([redacted] 1997) using a read-across approach.

We have assessed this information and identified the following issue:

A. Your read-across adaptation in accordance with Annex XI, Section 1.5. is rejected already for the reasons detailed in Section 1 of the Appendix on Reasons common to several requests.

B. Further to that, as noted in the Appendix on Reasons common to several requests, the results to be read across must have a reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

The corresponding test method to fulfil this information requirement is the OECD TG 201, along with the OECD GD 23 if the substance is difficult to test. On that basis, 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.

You provided a study according to the OECD TG 201 on the source substance where:

- 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 the OECD TG 201 are met.

Furthermore, the Substance is difficult to test (based on the OECD GD 23 indicator values of saturation concentration in aqueous media expected to be <100 mg/L, and hydrolysis half-life at 25°C and pH 7 of <24h) 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, your adaptation does not provide a reliable coverage of the key parameters of the corresponding OECD TG and it is rejected. On this basis, the information requirement is not fulfilled.

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

Study design

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

Appendix 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), unless a study according to OECD TG 422 is provided for Screening for reproductive/ developmental toxicity**

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. 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 2, 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).

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

The source of information (i) provides

- relevant information on the in-life observations;
- some relevant information on the blood chemistry as it informs on thyroid hormone levels but does not 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 of reproductive organd and kidneys, but does not cover the full scale of organs as expected in OECD TG 407/422.

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

However, the reliability of the sources of information (i) and (ii) provided with the analogue substances for this Substance is significantly affected by the deficiencies identified and explained under 'Appendix on Reasons common to several requests', Section 2. 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. Therefore, the sources are not considerd to reliaby inform on the key elements as foreseen to be investigated in OECD TG 407/422, and cannot contribute to the conclusion.

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.

In your comments to the draft decision, you indicate that you will conduct a sub-chronic (90 days) study (OECD TG 408) and fulfil the present information requirement by way of an adaptation based on Annex VIII, Section 8.6.1, Column 2, first paragraph, first indent. However, as this information is not yet available, 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. In addition, the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) can cover this information requirement.

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. Similarly, the present decision requests a Screening study for reproductive / developmental toxicity which can be conducted either according to the OECD TG 421 or according to the OECD TG 422. In case you decide to conduct the study according to the OECD TG 422, this study will also cover the short-term toxicity study (28 days) study information requirement.

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 of the standard information for this endpoint.

2. Screening for reproductive/developmental toxicity

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

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. 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)

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

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

As explained under Appendix on 'Reasons common to several requests', Section 2, 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 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

The studies referenced in CICAD (2009) review (source of information ii) on cyclic acid anhydride category may provide relevant information sexual function and fertility, toxicity to offspring, and systemic toxicity.

The source of information (i) provides relevant information on the key elements listed above.

However, the reliability of the sources of information (i) and (ii) provided with the analogue substances for this Substance is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests, Section 2. 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.

Based on above, while the source of information (i) provides relevant information and the source of information (ii) may provide relevant information, due to the deficiencies identified in the category approaches the sources are not considerd to reliaby inform for this Substance on the key elements as foreseen to be investigated in OECD TG 421/422 and, therefore, cannot contribute to the conclusion that the Substance has or has not the dangerous property investigated by the standard information requirement.

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 421/422, screening study. Therefore, your adaptation is rejected.

In your comments to the draft decision you agree that the Screening for reproductive/developmental toxicity study is a standard information requirement, and indicate your intention to use the pre-natal developmental toxicity study (Annex IX, Section 8.7.2; OECD TG 414), requested in the current draft decision, to adapt this information requirement.

ECHA points out that when the pre-natal developmental toxicity study is available, you may adapt this information requirement according to Annex VIII, Section 8.7.1, Column 2, first paragraph, fourth indent of REACH ("*this study does not need to be conducted if: [..] a pre-natal developmental toxicity study (Annex IX, 8.7.2) [..] is available*"). However, at this point in time, the study is still to be conducted.

Based on above, the information requirement is not fulfilled.

Study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[12] administration of the Substance.

3. 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 one OECD TG 203 study, and two internal lab protocol studies, with TPSA [1] in a read across approach as follows:
i. key study according to the 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:

A. Your read-across adaptation in accordance with Annex XI, Section 1.5. is already rejected for the reasons detailed in Section 1 of the Appendix on Reasons common to several requests,.

B. Further, as noted in the Appendix on Reasons common to several requests, the results to be read across must have a reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

The corresponding test method to fulfil this information requirement is the OECD TG 203, along with the OECD GD 23 if the substance is difficult to test. On that basis, 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

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

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.

You provided one key OECD TG 203 test, and two supporting short-term fish toxicity tests using internal lab protocols, on the source substance where:
- 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;
- 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.

Based on the above, the studies provided do not provide reliable information on short-term toxicity to fish as further detailed below:

The Substance is difficult to test (based on the OECD GD 23 indicator values of saturation concentration in aqueous media expected to be <100 mg/L, and hydrolysis half-life at 25°C and pH 7 of <24h)) 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, your adaptation does not provide a reliable coverage of the key parameters of the corresponding OECD TG and it is rejected. On this basis, the information requirement is not fulfilled.

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

Study design

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

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

1. 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 referring to Annex IX, Section 8.6.2, Column 2. 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, (octenyl)]. [….]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), key study
iii. A Hydrolysis as a Function of pH study (OECD TG 111) for the Substance ([redacted], 2012; 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, (octenyl)].*". 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 2 minutes at pH 7 (35°C). However, you have not provided any information on the hydrolysis rate of the Substance at lower pH present in the stomach following oral exposure. Therefore, you have not provided relevant data to demonstrate that the Substance would undergo immediate disintegration under physiological conditions.

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

Regarding 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 2. 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, your adaptation under Annex IX, section 8.6.2, column 2 is rejected, and the information provided does not fulfil the information requirement.

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

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[13]. The study should be performed with oral administration because the Substance is a liquid of low vapour pressure (43.5 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.

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; key study)
iii. Hydrolysis as a Function of pH study (OECD TG 111) for the Substance ([redacted] 2012; 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 adaptations.

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

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, (octenyl)-] 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*."

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[14] 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, you have considered the testing in the aqueous buffer; however, 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.

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 2, 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.

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

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 for this Substance is significantly affected by the deficiency identified and explained under the Appendix on 'Reasons common to several requests', Section 2. 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. 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 with a view to 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 the comments to the draft decision, you agree to perform the requested study.

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[15] 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 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, it is rapidly hydrolysed under environmentally relevant temperature and pH conditions (i.e., at pH 7, DT_{50}= 8.3 minutes at 15°C and DT_{50}= 4 minutes at 25°C). Each of these hydrolysis half-life values is substantially below the threshold half-life of 12 hours, below which "it can be assumed that the rate of hydrolysis is greater than that for uptake by exposed organisms" (Chapter R.7.c, "Endpoint-specific guidance",Guidance on information requirements and chemical safety assessment, ECHA, May 2008, Section R.7.10.3.4, p. 24). 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

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

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 the comments to the draft decision, you propose a tiered approach to fulfil this information requirement.

You present a testing strategy aimed at developing a read-across approach between the Substance and the source substance n-DDSA (EC: 243-296-9), for which there is a parallel compliance check decision. The testing strategy relies on the following information:

- Development of more robust data to further justify the analogue read-across approach.
  This includes verification of the physical-chemical properties and generation of data on algae growth inhibition and on short-term toxicity to fish and to *Daphnia* for the Substance (requests A.1, A.2 and B.3 in this decision) and for the source substance (requested by ECHA in a separate compliance check decision).
- Evaluation of all the data to verify if an analogue approach can be justified based on the RAAF requirements.
- Selection of the most appropriate substance (i.e. the Substance or the source substance) to conduct the requested study and, if deemed necessary, the study on long-term fish (request C.4).

You indicate that you will conduct the requested test with the Substance (as well as with the source substance) if the read-across approach cannot be justified.

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 Substance and for the source substance (including bridging studies and supporting information), no conclusion on the compliance of the proposed read-across adaptation can be made. You remain responsible for complying with this decision by the set deadline.

On this basis, the information requirement is not fulfilled.

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 substances 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 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, it is rapidly hydrolysed*

under environmentally relevant temperature and pH conditions (i.e., at pH 7, DT_{50}= 8.3 minutes at 15°C and DT_{50}= 4 minutes at 25°C). Each of these hydrolysis half-life values is substantially below the threshold half-life of 12 hours, below which "it can be assumed that the rate of hydrolysis is greater than that for uptake by exposed organisms" (Chapter R.7.c, "Endpoint-specific guidance",Guidance on information requirements and chemical safety assessment, ECHA, May 2008, Section R.7.10.3.4, p. 24). 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).

In the comments to the draft decision, you state further that: "*in view of REACH Article 25.1 (testing on vertebrate animals as a last resort) it is also preferred to wait for the results that will be obtained from the chronic studies with invertebrates* [request C.3]*, and data from the short-term fish studies* [request B.3]." You indicate that you will perform "*a new assessment based on the chronic data obtained with invertebrates and verify if a chronic fish study is still necessary*". 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. Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

Your adaptation is therefore rejected.

In the comments to the draft decision, you further propose a tiered approach to fulfil this information requirement.

You present a testing strategy (described under request C.3) aimed at developing a read-across approach between the Substance and the source substance n-DDSA (EC: 243-296-9), for which there is a parallel compliance check decision.

As explained under request C.3, no conclusion on the compliance of the proposed read-across adaptation can be made. You remain responsible for complying with this decision by the set deadline.

On this basis, the information requirement is not fulfilled.

Study design

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

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

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

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[16].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[17].

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

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

A. 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 F: Procedure

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

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

The compliance check was initiated on 28 August 2020.

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

ECHA took into account your comments and did not amend the requests.

Deadline to submit the requested information in this decision

You requested an extension of the deadline from 21 months specified in the decision to 36 months. You argue that the extension is needed for the tiered testing strategy proposed by you to generate information for the long-term aquatic toxicity endpoints (requests C.3 and C.4 above). You further indicate challenges in the development of analytical method and validation work for the aquatic toxicity studies due to the rapid hydrolysis of the Substance. Finally, you indicate possible delays because of limited capacity in the [redacted]

ECHA acknowledges that extra time may be needed to develop a suitable analytical method and providing an additional three months is considered as sufficient for that purpose. Further extension of the deadline is considered not justified. First, the proposed tiered testing strategy relies on a read-across approach that has not yet been fully described and justified, as explained in requests C.3 and C.4 above. Second, you have not provided any documentary evidence as requested by ECHA to substantiate your request based on the limited capacity in the [redacted].

On this basis, ECHA has extended the deadline by three months to 24 months.

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

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

Appendix G: List of references - ECHA Guidance[18] 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)[19]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[20]

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

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

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

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

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

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

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

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

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

OECD Guidance documents[21]

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

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

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

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

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

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

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

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

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