Helsinki, 19 August 2020

Addressee
Registrant of JS_94279-36-4 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
24 October 2016

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,2,4-BENZENETRICARBOXYLIC ACID, TRI-C9-11-ALKYL ESTERS
EC number: 304-780-6
CAS number: 94279-36-4

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

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***27 February 2023***.

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

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

2. Long-term toxicity testing on aquatic invertebrates also requested at C.3. below (triggered by Annex VII, Section 9.1.1., column 2);

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

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance;

2. Only if a negative result are obtained in the tests requested at A.1 and B.1 above, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

3. Justification for an adaptation of a Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1., column 2) based on the study requested at C.1 below;

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

5. Long-term toxicity testing on fish also requested at C.4 below (triggered by Annex VIII, Section 9.1.3., column 2);

C. Requirements applicable to all the Registrants subject to Annex IX of REACH

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

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance;

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

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance.

Conditions to comply with the requests

You are bound by the requests for information of this decision.

When a study is required under several Annexes of REACH, the reasons are provided in the corresponding appendices of this decision.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

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 general considerations

(i) Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28-day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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

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

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

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group (category) of 'Polyfunctional Acid Ester (PFAE) aromatic'. You have provided a read-across justification document in IUCLID Section 13.

For the purpose of this decision, the following abbreviations are used for the substances you list as category members:

TOTM Tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1);

DOTM 1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters, EC No. 290-754-9 (CAS No. 90218-76-1; former CAS No. 67989-23-5;

[2] ECHA Guidance R.6
[3] Read-Across Assessment Framework (RAAF)
[4] RAAF - considerations on multi-constituent substances and UVCBs

IDTM	Triisodecyl benzene-1,2,4-tricarboxylate, ED No. 253-138-0 (CAS No. 36631-30-8);
911TM	1,2,4-Benzenetricarboxylic acid, tri-C9-11-alkyl esters, EC No. 304-780-6 (CAS No. 94279-36-4); and
TM13	Triisotridecyl benzene-1,2,4-tricarboxylate, EC No. 276-594-2 (CAS No. 72361-35-4).

You provide the following rationale for the grouping:
"The substances are mono-constituents or mixtures of 1,2,4-Benzene tricarboxylic acid esters (UVCBs), which show a compositional variation regarding the length of the fattyalcohol side chains".

You define the applicability domain of the category as triesters of 1,2,4-Benzene tricarboxylic acid and linear fatty alcohols with a chain length ranging from C8 – C13.

You acknowledge that TOTM is not a member of the defined group but intend to be used as a supporting substance.

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

ii. 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, *"in identifying a category, it is important that all potential category members are described as comprehensively as possible"*, because the purity profile and composition can influence the overall toxicity/properties of the potential category members.[5] Therefore, qualitative and quantitative information on the compositions of the category members should be provided to confirm the category membership.

Furthermore, the provided information for categories consisting of UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substances needs to include qualitative compositional information of the individual constituents of the category members; 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]

Your read-across justification document contains compositional information for the members of your category. You have provided typical compositions of the category members in Table 2 of the read-across justification document.

The reported compositional information provided in the category justification document does not reflect the boundary composition of the corresponding REACH registrations. In addition, the compositional information on the Substance show that it contains significant amounts of both linear and branched alkyl chains. You have defined the applicability domain (see above) of the category in such a way that it only includes substances with exclusively linear alkyl chains. A significant portion of the Substance composition is outside of the applicability domain while you still list the Substance as a category member. Therefore the category membership of the Substance and all its constituents cannot be confirmed.

[5] ECHA Guidance Chapter R.6, Section R.6.2.4.1
[6] ECHA Guidance Chapter R.6, Section R.6.2.5.5

B. Predictions for (eco)toxicological properties

You have provided the following reasoning for the prediction of (eco)toxicological properties: *"Structural similarities of the category members results in similar physico-chemical properties. Given these similarities in structure and physico-chemical properties, it is reasonable to assume that the substances in the category will behave in a reasonably predictable manner regarding environmental fate and toxicity."*

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

You intend to predict the (eco)toxicological properties for the category members from information obtained from the source substance DOTM. You use TOTM as a "supporting substance" arguing that it is a suitable source study because it can hydrolyse to a known reproductive toxicant.

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

i. Missing Supporting information

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

Supporting information must include studies that allow side-by-side comparison of the ecotoxicological and toxicological properties of the Substance with those of the source substance(s); this includes information to confirm your hypothesis based on similarity in (eco)toxicological properties.

You have not provided any information on the Substance that would allow comparison of the toxicity profile of the Substance with that of the source substance. To support your read-across you have provided theoretical considerations on environmental fate, limited adsorption/bioavailability, and toxicokinetics.

In the absence of information on the Substance that allow a comparison of its toxicity profile with that of the source substance, ECHA is unable to verify your predictions based on your assumption that all substances have similar (eco)toxicological properties.

ii. 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 should:

- be adequate for the purpose of classification and labelling and/or risk assessment;

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

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

With regard to your predictions for *In vitro* gene mutation study in bacteria and Sub-chronic toxicity study (90-day), your source studies do not meet the above mentioned criteria (for details see the Appendix A, Section 1 and Appendix C, Section 1). ECHA concludes that the above mentioned critera are not met, and therefore no reliable predictions can be made for these information requirements.

iii. Bias of the prediction

In order to make an accurate prediction of ecotoxicological and toxicological properties all relevant infromation must be considered in the prediction. If not all infromation is considered in the read-across approach, then bias may be introduced in predictions. Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of source study(ies). If not all infromation that should have been considered has been considered then this may result in an over/under estimation in the prediction[8].

First, the Substance contains significant amounts of both linear and branched side chains. You provided source studies on DOTM (linear) and use TOTM (branched) as a "supporting substance" without explaining exactly what this means. Furthermore, you argue that TOTM is not a suitable source substance because it may hydrolyse to a known reproductive toxicant (2-ethylhexanol). The predictions currently used in the dossier do not consider the fact that the Substance has a significant amount of branched side-chains. Not considering information available on branched source substances may underestimate the hazard.

Second, you have not provided all relevant information on TOTM. In the registration dossier of TOTM there are additional studies which you have not considered for the predictions. These studies include a Sub-chronic toxicity study (OECD TG 408); Reproductive / developmental toxicity screening tests (OECD TG 421/422); a Pre-natal developmental toxicity study (OECD TG 414, modified to investigate endocrine disruptive properties); and several *in vitro/in vivo* mechanistic studies investigating estrogenic activity and anti-androgenic activity as well as gene expression of the neonatal testis following *in utero* exposure.

Third, you have not provided all relevant information on DOTM. In the registration dossier of DOTM there are additional studies which you have not considered for the predictions. These studies include a Sub-chronic toxicity study (OECD TG 408); and an *in vivo* mechanistic study as well as gene expression of the neonatal testis following *in utero* exposure.

Finally, you have provided a Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) conducted with Trioctylbenzene-1,2,4-tricarboxylate, EC No. 201-877-4 (CAS No. 89-04-3). This substance meets the criteria specified in your applicability domain, however you have not identified it as a category member, or explained why this substance has not been considered in your predictions for the Substance. Further more this study is not considered in your predictions for other endpoints, in particular repeated dose toxicity. In addition, there may be additional information available on the substance.

[8] RAAF, Section 4.5.1.5.

ECHA concludes that not all relevant information have been provided nor considered in your predictions. Therefore, ECHA considers that there is potential for bias in your predictions.

C. Assessment of the comments submitted on the Appendix on general considerations

In your comments on the draft decision, you acknowledge that the current read-across approach does not follow the Read-Across Assessment Framework (RAAF) standards and commit to revise the read-across justification. You also propose to refine the category and acknowledge that additional data is needed in the extremes of the category. You have provided a QSAR profiling report to support your approach.

QSAR Toolbox Profilers are not scientifically valid (Q)SAR models, and therefore the results from these Profilers cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, section 1.3 of REACH. QSAR Toolbox Profilers can be used to identify analogue substances and apply the grouping and read-across approach if the conditions under Annex XI, section 1.5. are fulfilled.

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).[9]

You have provided neither a justification for a read-across adaptation (hypothesis and explanation of the rationale for the predictions), nor robust study summaries of studies conducted with identified analogue substances.

ECHA acknowledges your intention to strengthen the read-across approach. However, without further details on composition of the substances intended to be included in the category, detailed results of all studies, and the improved read-across justification, ECHA is unable to assess whether or not the new approach would comply with the Annex XI, Section 1.5. requirements.

D. Conclusions on the read-across approach

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

[9] ECHA Guidance R.6, Section R.6.2.6.1

Appendix A: Reasons for the requests to comply with Annex VII of REACH

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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

You have provided:

i. [redacted] 1987 – Key study; Bacterial reverse mutation assay (similar to OECD TG 471) conducted with tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate, EC No. 268-007-3 (CAS No. 67989-23-5; DOTM) using the following strains, *S.typhimurium* TA 97, TA 98, and TA 100, which all gave negative results.

ii. [redacted] 1996 – Supporting study; Bacterial reverse mutation assay (OECD TG 471) conducted using Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1; TOTM), using the following strains, *S.typhimurium* TA 98, TA 100, TA 1535, and TA 1537; and *E. coli* WP2 uvrA, which all gave negative results.

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected.

As indicated in the Appendix on general considerations, there are issues with adequacy and reliability of source studies, and these are assessed directly below.

If the grouping concept is applied to an *In vitro* gene mutation study in (OECD TG 471) then the results from the source study to be read across should:

- have adequate and reliable coverage of the key parameters addressed in the OECD TG 471. Specifically, the test must be performed with five strains: four strains of S. *typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The source study was was not conducted using the five required strains; results in TA1535 or TA1537; and TA102, E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) are missing.

In your comments on the draft decision, you agree to conduct the test with the Substance.

On this basis, the information requirement is not fulfilled.

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

2. Long-term toxicity testing on aquatic invertebrates also requested at C.3 below (triggered by Annex VII, Section 9.1.1., column 2)

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

water soluble substances (e.g. water solubility below 1 mg/L) long-term toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5) must be considered instead of an acute test. Poorly water soluble substances require longer time to reach steady-state conditions and the short-term tests may not give a true measure of toxicity for this type of substances.

The based on the information in your dossier, the Substance is poorly water soluble (water solubility below 0.05 mg/L).

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

The examination of the adaptation, as well as the selection of the requested test and the test design are addressed in Appendix C, section 3.

In your comments on the draft decision you agreed to conduct the study the Substance.

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

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

You have provided:

i. [redacted] 1994 - Algal Inhibition test (EU Method C.3), GLP compliant, conducted using analogue substance Tri-n-C8,C10-alkyl trimellitate, CAS 90218-76-1.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you agreed to conduct the study with the Substance.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, Freshwater Alga and Cyanobacteria, Growth Inhibition Test (test method OECD TG 201) is considered suitable.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. **In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided:

i. [redacted] 1996 – Supporting study, In vitro mammalian chromosome aberration test (similar to OECD TG 473) conducted using Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1; TOTM) which gave negative results.

ii. [redacted] 2009 – Key study, In vitro mammalian chromosome aberration test (OECD TG 473) conducted using tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate, EC No. 268-007-3 (CAS No. 67989-23-5; DOTM; i.e. the source substance) which gave negative results.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

In your comments on the draft decsion, you agree to conduct the test with the Substance.

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

2. **Only if a negative result are or obtained in the tests requested at A.1 and B.1 above, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

You have provided:

i. [redacted] 1985 – Supporting study, In vitro mammalian cell gene mutation test (similar to OECD TG 476) conducted using TOTM which gave negative results.

ii. [redacted] 2009 – Key study, In vitro mammalian cell gene mutation test (OECD TG 476) conducted using DOTM which gave negative results.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In your comments on the draft decision, you propose to adapt this information requirement using the revised read-across approach.

As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

The result of the requests for information in Appendix A, Section 1 and Appendix B, Section 1 will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered. Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria, and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide negative results.

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Justification for an adaptation of the Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1., column 2)

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

You have provided:

i. [redacted] 1996 – Supporting study, Repeated Dose 28-Day Oral Toxicity in Rodents (similar to OECD Guideline 407) conducted in rats with TOTM (oral gavage) using the doses of 100, 300 and 1000 mg/kg/day. A NOAEL >1000 mg/kg/day is reported based on no adverse effects.

ii. [redacted] 2010 – Key study, Repeated Dose 28-Day Oral Toxicity in Rodents (OECD Guideline 407) conducted in rats with DOTM (oral gavage) using the doses of 100, 300 and 1000 mg/kg/day. A NOAEL 300 mg/kg/day is reported based body weight and hair loss.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In your comments on the draft decision, you propose to adapt this infromation requirement using the revised read-across approach.

As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

The present decision requests the registrants concerned to generate and submit a reliable Sub-chronic toxicity study (90 days) (see Appendix C, Section 1). According to Column 2 of Annex VIII, Section 8.6.1. an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available. For that reason, and in order to prevent unnecessary animal testing, a short term toxicity study (28 days) does not need to be conducted. To ensure that you 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.

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

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. No such evidence is available in your dossier.

You have provided:

i. [redacted] 2001 – Key study, Combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (OECD TG 422) conducted using trioctyl benzene-1,2,4-tricarboxylate, EC No. 201-877-4 (CAS No. 89-04-3), NOEL 500 mg/kg/day.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In your comments on the draft decision, you propose to adapt this information requirement using the revised read-across approach.

As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Specifications for the 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[10] administration of the Substance.

5. Long term toxicity testing on fish also requested at C.4. below (triggered by Annex VIII, Section 9.1.3., column 2)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH. However, pursuant to Annex VIII, section 9.1.3, column 2, for poorly water soluble substances (e.g. water solubility below 1 mg/L) long-term toxicity study on fish (Annex IX, Section 9.1.6) must be considered instead of an acute test.

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

The based on the information in your dossier, the Substance is poorly water soluble (water solubility below 0.05 mg/L).

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

The examination of the adaptation, as well as the selection of the requested test and the test design are addressed in Appendix C, Section 4.

Your comment submitted for this request is addressed in Appendix C, Section 4.

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

Appendix C: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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

You have provided:

i. [redacted] 1996 – Supporting study, Repeated Dose 28-Day Oral Toxicity in Rodents (similar to OECD Guideline 407) conducted in rats with Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1; TOTM) (oral gavage) using the doses of 100, 300 and 1000 mg/kg/day. A NOAEL >1000 mg/kg/day is reported based on no adverse effects.

ii. [redacted] 2010 – Key study, Repeated Dose 28-Day Oral Toxicity in Rodents (OECD Guideline 407) conducted in rats with tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate, EC No. 268-007-3 (CAS No. 67989-23-5; DOTM; i.e. the source substance) (oral gavage) using the doses of 100, 300 and 1000 mg/kg/day. A NOAEL 300 mg/kg/day is reported based body weight and hair loss.

We have assessed this information and identified the following issues:

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In your comments on the draft decision, you propose to adapt this information requirement using the revised read-across approach.

As explained in the Appendix on general considerations your adaptation is rejected.

As indicated in the Appendix on general considerations, there are issues with adequacy and reliability of source studies, and these are assessed directly below.

If the grouping concept is applied to a Sub-chronic toxicity study (90-day; OECD TG 408) then the results from the source study to be read across must have adequate and reliable coverage of the key parameters addressed in the OECD TG 408. Specifically: the study number of animals must be at least 10 per sex per dose group; and exposure duration of 90-day or longer.

The source study was conducted with 5 rats per sex per dose group compared to 10 rats per sex per dose group required by the OECD TG 408. Thus, the statistical power of the source study is insufficient. Furthermore, the source study does not have the required exposure duration of 90 days as required in OECD TG 408.

On this basis, the source study does not fulfil the information requirement.

Specifications for the study design

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 toxicityand the prefered

rodent species is rat[11]. 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 (Annex IX, Section 8.7.2.) in a first 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:

i. [redacted] 2010 – Key study, Pre-natal developmental toxicity study (OECD TG 414) conducted in rats with DOTM (oral gavage) using the doses of 100, 300 and 1000 mg/kg/day. LOEL for maternal toxicity 1000 mg/kg/day is reported based on (-67% body weight gain). NOAEL for foetal effects 1000 mg/kg/day is reported based -12% pup weight (other teratogenic effects insufficiently reported).

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In your comments on the draft decision, you propose to adapt this information requirement using the revised read-across approach. As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Specifications for the 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[12] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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

You have provided:

i. [redacted] 1997 - *Daphnia magna* reproduction test (OECD Guideline 202, part II adopted in 1984), GLP compliant, conducted using DOTM.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is considered suitable.

In your comments on the draft decision you agreed to conduct the study with the Substance.

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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

[11] ECHA Guidance R7a, Section R.7.5.6.3.2 and Table R.7.5-1
[12] ECHA Guidance R.7a, Section R.7.6.2.3.2

REACH Regulation.

You have adapted this information requirement by using Column 2 of Annex IX Section 9.1, claiming that the chemical safety assessment does not indicate the need to investigate further the effects on fish.

To adapt the information requirement for long-term toxicity testing on fish based on Annex IX, Section 9.1, Column 2, the Chemical Safety Assessment (CSA) needs to assess and document that risks arising from the Substance are controlled (Annex I, Section 0.1 to the REACH Regulation).

In particular, you need to take into account environmental hazard assessment including classification and labelling and identification of PNEC, as described in Annex I to the REACH Regulation.

For the purpose of hazard assessment, the available toxicity information should at least cover species of three trophic levels: algae/aquatic plants, invertebrates (Daphnia preferred), and fish. Regarding long-term toxicity testing, there are no further requirements for fish testing if there is compelling evidence to suggest that the fish is likely to be at least a factor of about 10 less sensitive than invertebrates or algae. In case the relative sensitivity of fish cannot be predicted, further testing is needed.[13]

For hydrophobic/poorly water soluble substances, short-term toxicity studies cannot constitute the compelling evidence to indicate a lack of effects in the long-term studies nor to predict relative species sensitivity. Hydrophobic/poorly soluble substances require longer time to be significantly taken up by the test organisms and in consequence the steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for this type of substances.

The Substance is an organic UVCB for which you reported a calculated logP value of 10.60 and is therefore hydrophobic.

You have provided short-term toxicity studies on fish, *Daphnia* and algae, and a long-term toxicity study on *Daphnia* with DOTM. No effects were observed in these studies.

You argue that no long-term fish toxicity study is needed because no effects up to the limit of the water solubility was observed and because fish cannot be identified as the most sensitive taxonomic group based on the short-term values.

Because the Substance is hydrophobic and no effects were observed in the short-term tests, the short-term toxicity data cannot be used to reliably predict the relative species sensitivity. Furthermore, the data was generated with an analogue substance and as described in the Appendix on general considerations your read-across adaptation is rejected. Therefore you have not provided compelling evidence to predict the relative sensitivity of fish.

In conclusion long-term testing on fish is needed for the CSA to document that risks to the aquatic environment are controlled.

[13] ECHA Guidance R.7b, Section R.7.8.5.3

In your comments on the draft decision, you state that you intend to adapt this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on general considerations your adaptation is rejected.

In addition, ECHA notes the following:
Under REACH for proper CSA, aquatic toxicity data on species from at least three different trophic levels (algae, invertebrates and fish) are required (Annex VII to IX in conjunction with Annex I).

In your comments to the draft decision, you proposed to use the long-term *Daphnia* study (OECD TG 211) as bridging study to support your intended read across for the long-term fish study (OECD TG 210).

ECHA considers that there is no scientific justification to substantiate your assumption that fish would be equivalently or even less sensitive to the Substance than aquatic invertebrates. In the literature, many studies are available that have attempted to compare the sensitivities of fish and *Daphnia* to chemical substances[14, 15] and have repeatedly shown that none of both trophic levels can be regarded as generally more sensitive in acute or long-term testing.

The sensitivity of a species depends on mechanistic factors like the mode of action of the substance, its metabolism, toxico-kinetics. Those factors depend both on the test species and on the chemical substance. Fish and aquatic invertebrates are from different taxonomic groups. They have very different types of physiology, metabolism and toxicokinetics, so they may have different sensitivities to the Substance.

In addition, as explained above the Substance is hydrophobic and poorly water soluble and short-term data cannot be used to reliably estimate the sensitivity of aquatic organisms to the Substance. Therefore to complete the Chemical Safety Assessment (CSA) under REACH, it is necessary to conduct long-term studies on three trophic levels, aquatic plants, invertebrates and fish. Both the study on long-term toxicity to aquatic invertebrates and fish are hence required to complete the CSA.

On this basis, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is considered suitable.

As indicated above, the preferred test method to cover this information requirement under REACH is the OECD TG 210. In addition, please note that OECD GD 210 indicates that for difficult to test substances, the OECD Guidance Document No. 23 should be consulted.

[14] E.g. Cairns, J Jr. The Myth of the Most Sensitive Species. BioScience Vol. 36, No. 10 (Nov., 1986), pp. 670-672.
[15] https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte_87_2015_comparison_of_species.pdf

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 6 September 2018.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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

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

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

Appendix E: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

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

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

   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: 'How to report robust study summaries'[16].

4. Test material

   Selection of the test material(s)

   While selecting the test material you must take into account 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.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[17].

5. List of references of the ECHA Guidance and other guidance/ reference documents[18]

   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 in this decision.

[16] https://echa.europa.eu/practical-guides
[17] https://echa.europa.eu/manuals
[18] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[19]

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.

OECD Guidance documents[20]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[19] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[20] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.