EUROPEAN CHEMICALS AGENCY

Helsinki, 19 August 2020

Addressees
Registrants of JS_72361-35-4 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: TRIISOTRIDECYL BENZENE-1,2,4-TRICARBOXYLATE
EC number: 276-594-2
CAS number: 72361-35-4

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 ***29 May 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 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.; 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; with the Substance;

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

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;

When a study is required under several Annexes of REACH, the reasons are provided in the corresponding appendices of this decision. The registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants in accordance with Article 53 of REACH.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

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.

EUROPEAN CHEMICALS AGENCY

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. First, 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. Second, 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);
IDTM	Triisodecyl benzene-1,2,4-tricarboxylate, ED No. 253-138-0 (CAS No. 36631-30-8);

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

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 fatty alcohol 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 use it 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.

B. Predictions for (eco)toxicological properties

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

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;
- 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.

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

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 conclude that the above mentioned critera are not met; 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 consdered has been considered then this may result in an over/under estimation in the prediction[8].

First, the Substance contain significant amounts of both linear and branched side chains. You provide source studies on DOTM (linear) and use TOTM (branced) 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, in the registration dossier of 911TM, there is 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.

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

[8] RAAF, Section 4.5.1.5.

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 you indicate your intention to strengthen the read-across approach.

ECHA acknowledges your intention to strengthen the read-across approach and that the Substance addressed in this decision is one of the intended source substances of the category.

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.

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; i.e. the source substance) 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 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.

Therefore, the information requirement is not fulfilled.

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

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.

Your comment on the draft decision submitted for the request of long-term toxicity testing on aquatic invertebrates is addressed in Appendix C, Section 3.

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 tris(mixed decyl and octyl)benzene-1,2,4-tricarboxylate, CAS 90218-76-1, EC 290-754-9.

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 decision you agreed to conduct the study on the Substance.

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 decision you agreed to conduct the study 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. As explained in the Appendix on general considerations your adaptation is rejected. Therefore, 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.

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

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. 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 decision you agreed to provide an adaptation based on the results form the requested 90-day study.

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.

You have not provided a robust study summary for this endpoint. Instead, you have adapted the information requirement using what ECHA understands to be weight of evidence approach (Annex XI, Section 1.2). In your justification the following independent sources of information are presented:

- results from Repeated dose toxicity study in rats (OECD TG 407) conducted with DOTM;
- the fact that a testing proposal for Sub-chronic toxicity study (OECD TG 408) to be conducted with DOTM; and
- the fact that these studies sufficiently cover male and female reproductive organs

Based on the presented lines of evidence you argue that no further testing on reproduction toxicity is necessary.

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

The sources of information provided in your weight of evidence adaptation must cover the key elements (parameters) foreseen to be investigated in an OECD TG 421/422 study these include screening level infromation on 'functional fertility' in the P generation and 'effects on the offspring' in the F1 generation.

However, none of the sources of information that you provided have any information on 'functional fertility' in the P generation and 'effects on the offspring' in the F1 generation.

In addition, you have not provided any information generated using the Substance. As explained in the Appendix on general considerations your read-across adaptation is rejected. Consequently, information generated on DOTM is not relevant for the hazard identification of the Substance.

In your comments on the draft decision, you propose not to conduct this study. Instead you proposed to adapt this infromation requirement based the Pre-natal developmental toxicity study and the Sub-chronic toxicity study (OECD TG 408) requested in this decision. The OECD TG 408 is proposed to include additional parameters on reproductive organs. Your comment on the proposed additional parameters is addressed in Appendix C, Section 1.

A Reproduction/developmental toxicity screening test (OECD TGs 421 or 422) is a standard information requirement at REACH Annex VIII level. Since the Column 1 requirements in the REACH Annexes are cumulative, a screening test should also be available at REACH Annex IX and X level. However, if a Pre-natal developmental toxicity study, a Two-generation reproductive toxicity study or an Extended one-generation study is available, the screening study can be omitted based on REACH Annex VIII, Section 8.7.1., Column 2 adaptation rules. Currently, there are no Pre-natal developmental toxicity, Two-generation reproductive toxicity or Extended one-generation studies available. Therefore, the Column 2 adaptation rules are not met.

According to ECHA Guidance R.7a, it is strongly recommended to perform the screening study in cases where an Extended one-generation study is not triggered at Annex IX. As detailed in that Guidance with the modified OECD TG 408, the investigations of fertility would be limited to evaluation of reproductive organs; i.e. all functional fertility parameters of the screening study would be missing. As an alternative, you may consider combining the OECD TG 408 and the OECD TG 421.

On this basis, your adaptation is rejected and 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[9] 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.

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 on the draft decision submitted for the request of long-term toxicity testing on fish is addressed in Appendix C, Section 4.

[9] 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:

A. 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 a Sub-chronic toxicity study (90-day; OECD TG 408) 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 408. Specifically:
   - the study number of animals must be at least 10 per sex per dose group; and
   - exposure duration of 90 days 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.

In your comments on the draft decision, you agree to conduct the study on the Substance and propose to "*include additional endpoints allowing for the evaluation of the reproductive system of male (testis, epididymis, prostate, coagulating gland and seminal vesicles) and female (ovary, uterus and vagina))*".

However, the listed "additional endpoints" as histopathological examinations of these tissues are mandatory in the OECD TG 408.
ECHA considers that additional parameters related to reproductive toxcicity which could be included in an OECD TG 408 are investigations of sperm parameters and oestrus cycle (as specified in the Two-generation reproductive toxicity study test guideline; OECD TG 416, paragraphs 28-33). You may include these investigations at your own discresion.

Therefore, 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[10]. 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. 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 decision you agreed to conduct the study on the Substance.

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[11] 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.

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

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

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

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 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).

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

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.[12]

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.

In your comments on the draft decision, you stare that you intend to adapt this information requirement by using a Grouping of substances and read-across approach under Annex XI,

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

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). You also refer to an UBA repeprt regarding species sensitivity.

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[13]. Those studies, as well as the UBA report[14] cited in your comments 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, and its toxicokinetics. 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.

[13] E.g. Cairns, J Jr. The Myth of the Most Sensitive Species. BioScience Vol. 36, No. 10 (Nov., 1986), pp. 670-672.
[14] 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'[15].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   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"[16].

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

5. List of references of the ECHA Guidance and other guidance/ reference documents[17]

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.

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)[18]

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[19]
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.

[17] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[18] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[19] 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.