EUROPEAN CHEMICALS AGENCY

Helsinki, 19 August 2020

Addressees
Registrants of CEM JS 36631-30-8 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
28 February 2013

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: TRIISODECYL BENZENE-1,2,4-TRICARBOXYLATE
EC number: 253-138-0
CAS number: 36631-30-8

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

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

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; with the Substance;

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1., column 2; 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.

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.

EUROPEAN CHEMICALS AGENCY

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

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

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. Description of the read-across approach

You have provided a read-across justification in an Appendix to the CSR.

You read across from the structurally similar source substances:

TOTM 1,2,4-benzenetricarboxylic acid, tris (2-ethylhexyl) ester; 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; and

911TM Trioctylbenzene-1,2,4-tricarboxylate, EC No. 201-877-4 (CAS No. 89-04-3)

to the Substance.

You argue that the substances are structurally similar and have similar physicochemical properties and due to that they have the same functional group they are expected to have similar (eco)toxicological properties.

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

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.

In your revised read-across justification attached to your comments on the draft decision you confirm ECHA's understanding.

B. Predictions for (eco)toxicological properties

i. Read-across hypothesis

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[5]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure, functional groups and physicochemical properties between the source substances and the Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

Similarity in chemical structure and similarity of some of the physicochemical properties does not necessarily lead to predictable or similar ecotoxicological or toxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the category members.

In your comments on the draft decision, you have provided a revised read-across justification. In this justification you indicate that the Substance is member of category known as "Fatty acid esters" consisting of 12 substances.

In your revised read-across hypothesis you refer to RAAF scenario 4, i.e. category approach for which the read-across hypothesis is based on different compounds with qualitatively similar properties. Then you limit the discussion to TOTM, DOTM, 911TM and the Substance. In the actual predictions you limit it even further only employing a one-to-one read-across from TOTM (this would be RAAF scenario 2). You need to develop and provide one coherent read-across hypothesis and then use that thoughout the documentation. Without a clear hypothesis ECHA is unable to assess whether or not the new approach would comply with the Annex XI, Section 1.5. requirements.

In addition, your read-across revised hypothesis is that the (eco)toxicological similarity between the source substance(s) and your Substance in one or multiple endpoints is a sufficient basis for predicting the properties of your Substance for other endpoints, i.e. there is a consistent pattern of effects for the (eco)toxicological properties addressed in this decision.

You have not provided a well-founded hypothesis to establish a reliable prediction for the (eco)toxicological properties addressed in this decision, based on recognition of the structural similarities and differences between the source substance(s) and your Substance, and linking these similarities/differences to a consistent pattern of (eco)toxicological effects.

ii. Missing Supporting information

[5] ECHA Guidance, Chapter R.6.

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*"[6]. 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 or worst-case prediction.
You have not provided any supporting information on the Substance that is comparable with the infromation on the source substance for the infromation requiremnts covered by read-across.

In the absence of (eco)toxicological infromation on the Substance that allow comparison with that of the source substance, ECHA is unable to verify your predictions of similar toxicity and your assumption of a worst-case prediction. ECHA concludes that you have not provided sufficient information to support the rationale for the read-across.

In your revised read-across justification, you have included additional considerations with regard to substance characterisation, structural similarities and differences between the source substances and the Substance, and attempted to link the structural similarities/differences to the proposed regular pattern of quantitatively and qualitatively similar effects.

Data matrix

As indicated above, your revised read-across hypothesis assumes that different compounds have quantitatively and qualitatively similar properties and that there is a consistent pattern of effects for the (eco)toxicological properties addressed in this decision.

In this context toxicodynamic information must include the qualitative properties (i.e. the type of effect(s) observed) and the quantitative properties (i.e. the effect size). To assess consistency in quantitative terms the effect size, i.e. LO(A)EL(s) are needed. Furthermore, the LO(A)EL(s) has to be combined with a description of the actual effect(s) observed. Otherwise the consistency in qualitative terms can not be assessed.

To support consistency of effects you have provided a data matrix covering the REACH information requiremnts.

The information provided in your comment is limited to a NOAEL and whether the study is proposed to be read-across or if it is actual data on a substance.

This amount of information is not sufficient to assess consistency of effects nor to identify a consistent pattern.

In conclusion, based on the documentation provided it is not possible to assess whether or not the substances within the group have a consistent pattern of effects across the (eco)toxicologial properties addressed in this decision.

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

Information on potental metabolites

As indicated above, your revised read-across hypothesis assumes that different compounds have quantitatively and qualitatively similar properties and that there is a consistent pattern of effects for the (eco)toxicological properties addressed in this decision.

In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substance(s) may support the formation of the common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

In addition, the outcome of a (eco)toxicological test is the sum of all effects caused by the substance itself and its metabolites. In order to support a consistent pattern of (eco)toxicological effects using a toxicokinetic argumentation the vast majority of the substances would need to have toxicokinetic data demonstrating to what extent each metabolite is formed. Furthermore, each metabolite would need (eco)toxicological information corresponding to the information requirements under consideration. In addition, if the parent compound is not rapidly metabolised, then also the contribution to (eco)toxicity from the parent coumpound would need to be addressed.

In the comments on the draft decision, you have provided additional information on likely metabolites of the substances in order to support your hypothesis. However, you have not provided toxicodynamic information on the metabolites.

Therefore, ECHA is unable to assess to what extent this information support your read-across hypothesis.

C. 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] 2008 – Key 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; i.e. the source substance), 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.

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 test with the Substance.

2. 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 a study by [redacted] 1998– Key study, performed according to OECD TG 201 (Alga, Growth Inhibition Test), conducted with TOTM.

You have adapted this information requirement by using a 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, the Freshwater Alga and Cyanobacteria, Growth Inhibition Test (OECD TG 201) is considered suitable.

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

3. 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, pursuant to Annex VII, section 9.1.1, column 2, for poorly water soluble substances long-term toxicity study on *Daphnia* (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.

Based on the information in your dossier the Substance is highly hydrophobic (log Kow >9.4 at 35 deg C) which indicates that it has low water solubility.

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 *Daphnia* is addressed in Appendix C, Section 3.

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] 2008 – Key study, In vitro mammalian chromosome aberration test (OECD TG 473) conducted using Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1; TOTM; 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 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 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] 2008 – Key study, In vitro mammalian cell gene mutation test (OECD TG 476) conducted using TOTM 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 provide further arguments to enhance your 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 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. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided:

i. [redacted] 2012 – Key study, Repeated Dose 90-Day Oral Toxicity in Rodents (OECD Guideline 408) conducted in rats with TOTM (oral gavage) using the doses of 50, 225 and 1000 mg/kg/day. A NOAEL 225 mg/kg/day is reported based on changes in clinical chemistry, liver and spleen weight and histopathology.

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 provide further arguments to enhance your read-across approach.

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

On this basis, the information requirement is not fulfilled.

Column 2 of Annex VIII, Section 8.6.1., provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.
The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Appendix C, Section 1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted. Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

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 provided:

i. [redacted] 2001 – Key study, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity (OECD Guideline 422) conducted in rats with trioctyl benzene-1,2,4-tricarboxylate EC No. 201-877-4 (CAS No. 89-04-3; TOTM), using the doses of 30, 125 and 500 mg/kg/day. A NOAEL >500 mg/kg/day for the general toxicity and a NOAEL >500 mg/kg/day for the reproductive/developmenal is reported.

ii. [redacted] 1998 – Supporting study, Reproduction /

Developmental Toxicity Screening Test (OECD Guideline 421) conducted in rats with TOTM using the doses of 100, 300 and 1000 mg/kg/day. A reproductive NOAEL >1000 mg/kg/day for the P generation and developmental NOAEL >1000 mg/kg/day for the F1 generation is 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 provide further arguments to enhance your 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[7] 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 highly hydrophobic (log Kow >9.4 at 35 deg C) which indicates that it has low water solubility.

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.

[7] 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] 2012 – Key study, Repeated Dose 90-Day Oral Toxicity in Rodents (OECD Guideline 408) conducted in rats with Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC No. 222-020-0 (CAS No. 3319-31-1; TOTM; i.e. the source substance) (oral gavage) using the doses of 50, 225 and 1000 mg/kg/day. A NOAEL 225 mg/kg/day is reported based on changes in clinical chemistry, liver and spleen weight and histopathology.

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 provide further arguments to enhance your 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

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[8]. 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. EPA TSCATS low detail report, 2002/ Report prepared for US Consumer Product Safety Commission, 2010 – Key study, Pre-natal developmental toxicity study (OECD TG 414) conducted in rats with TOTM (oral gavage) using the doses of 100, 500 and 1050 mg/kg/day. NOEL for maternal toxicity 1050 mg/kg/day is reported based on no effects. NOEL for developmental effects 500 mg/kg/day is reported based on retained areolar regions in male offspring on evaluation at post-natal day 13 at 1050 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 provide further arguments to enhance your read-across approach.
As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

[8] ECHA Guidance R7a, Section R.7.5.6.3.2 and Table R.7.5-1

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[9] 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] 1998 – Key study, "*Daphnia magna* Reproduction Test" (OECD TG 211) conducted with TOTM.

You have adapted this information requirement by using a 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 on 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 REACH.

You have provided:
i. [redacted] 1998 – Key study, "Fish, Prolonged Toxicity Test: 14-day Study" (OECD Guideline 204) conducted with TOTM.

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 addition to the arguments presented in the Appendix on general considerations, you have not provided an adequate and reliable source study for this information requirement.

If the grouping concept is applied to long-term toxicity on fish, only studies where sensitive life-stages (juveniles, eggs, larvae) are exposed to the test material can be considered. The preferred test method to cover this information requirement under REACH is the OECD TG 210[10]. The source study to be used for read-across for this endpoint must have adequate and reliable coverage of the key parameters addressed in the OECD TG 210. Specifically:
- observation of the stage of embryonic development, hatching success and post-hatch survival, abnormal appearance/ behaviour, weight and length of surviving animals, and
- cover an exposure duration of 30 days post-hatch as required for *Oryzias latipes*.

The provided source study was conducted according to OECD TG 204 and addresses only mortality of adult/juvenile fish. Therefore it does not cover the key parameters as required

[9] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[10] ECHA Guidance R.7b, Section R.7.8.2

by OECD TG 210. Furthermore, the source study does not have the required exposure duration (14 days test duration only).

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). You also refer to an UBA report 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[11]. Those studies, as well as the UBA report[12] cited in your comments have repeatedly shown that neither trophic level 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.

In addition please note that as specified in OECD TG 210, for difficult to test substances, the OECD Guidance Document No. 23 should be consulted.

[11] E.g. Cairns, J Jr. The Myth of the Most Sensitive Species. BioScience Vol. 36, No. 10 (Nov., 1986), pp. 670-672.
[12] 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'[13].

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"[14].

[13] https://echa.europa.eu/practical-guides
[14] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[15]

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)[16]

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[17]
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.

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