Helsinki, 18 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114382253-51-01/F
Substance name: Esterification products of 1,3-dioxo-2-benzofuran-5-carboxylic acid with nonan-1-ol
List number: 941-303-6
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15.12.2014
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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

2. **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 registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that both studies requested under points 1 and 2 of this decision have negative results;**

4. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

5. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**

6. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

7. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

8. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method: EU C.7./OECD TG 111) with the registered substance;**

9. **Activated Sludge, Respiration Inhibition Testing (Annex VIII, Section 9.1.4.;test method: activated sludge, respiration inhibition test (Carbon and Ammonium Oxidation, OECD TG 209) with the registered substance;**

10. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance, including the sex-ratio parameter;**

11. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test methods: Fish, early-life stage (FELS) toxicity test, OECD TG 210 or OECD TG 234 Fish sexual developmental test) with the registered substance;**

12. **Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: DOC die-away test, OECD TG 301A) or Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: CO2 evolution test, OECD TG 301B) or Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: MITI test (I), OECD TG 301C) or Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Closed bottle test, OECD TG 301D) or Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Modified OECD screening test, OECD TG 301E) or Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Manometric respirometry test, OECD TG 301F) with the registered substance;**

13. **Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: Aerobic and anaerobic transformation in soil, EU C.23./OECD TG 307) at a temperature of 12 °C with the registered substance;**

14. **Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: Aerobic and anaerobic transformation in aquatic sediment systems, EU C.24./OECD TG 308) at a temperature of 12 °C with the registered substance;**

15. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance ;**

16. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305, aqueous exposure/dietary exposure with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***25 June 2021*** except for the information requested under point 4 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **3 January 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 5 after ***25 March 2019***, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

0. 1. Grouping of substances and read-across approach

Your registration dossier contains adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation, for the following endpoints:

- *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.)
- *In vitro* cytogenicity in mammalian cells (Annex VIII, 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.)
- Sub-chronic toxicity (90-day) study (Annex IX, 8.6.2.)
- Pre-natal developmental toxicity study (Annexes IX and X, 8.7.2.)
- Activated Sludge respiration Inhibition test (Annex VIII, 9.1.4.)
- Long term toxicity test to aquatic invertebrates (Annex IX, 9.1.5.)
- Long term toxicity test to Fish (Annex IX, 9.1.6.1.)
- Ready biodegradability (Annex VII, 9.2.1.1.)
- Bioaccumulation in aquatic species (Annex IX, 9.3.2.)

ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 to 4, 6-7, 9 to 12, and 16 below).

a) ECHA assessment

You have sought to adapt the information requirements for the endpoints listed above by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, 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 (read-across approach). Furthermore, Annex XI, Section 1.5. lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

You consider to achieve compliance with the REACH information requirements for the registered substance TM9 (Esterification products of 1,3-dioxo-2-benzofuran-5-carboxylic acid with nonan-1-ol; EC number 941-303-6) using data of three structurally similar substances, namely

- TM8 (Trioctyl benzene-1,2,4-tricarboxylate): EC number 201-877-4 and CAS RN 89-04-3,
- TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester): EC numbers 290-754-9 / 268-007-3 and CAS RN 90218-76-1,
- TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate): EC number 222-020-0 and CAS RN 3319-31-1,

(hereafter the 'source substances').

You have provided read-across documentation as a separate attachment. You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: "*the* [registered] *substance is regarded as part of a defined group, comprising a family of chemicals synthesised by esterifying trimellitic anhydride with alcohols in the presence of an acid catalyst. Trimellitates in this category are all 1,2,4-benzenetricarboxylic acids with side chain ester groups ranging from C8 to C10. The structural formula for trimellitates varies depending on the isomeric composition of the alcohols used in their manufacture. The specific trimellitate esters considered are products derived from 2-ethylhexanol, octanol, and a mix of octanol and decanol. Because of the similarity in chemical structure and common degradation – hydrolysis to the di-ester, then mono-ester then further hydrolysis to yield trimellitic acid and the corresponding alcohol - it is considered that the physico-chemical and (eco)toxicological properties of the substances in this category will be similar."* You propose that the source and registered substances have similar properties for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis.

b) ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties between the source and target substances is a sufficient basis for predicting the properties of the substance. This argument is limited and is in principle not capable of being sufficient. Similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that similarity in structure/ physico-chemical/ ecotoxicological/ toxicological properties *per se* is sufficient to enable you to predict the human health and environmental properties of your substance as listed above. This is because similarity in structure and physico-chemical properties do not always lead to predictable or similar human health/ environmental properties. Further elements are needed[2], such as a well-founded hypothesis of (bio)transformation to a common compound(s), or that different compounds have the same type of effect(s), to allow a prediction of human health/ environmental properties that does not underestimate risks.

You have also proposed that similarity in common degradation provides a basis for predicting the properties of the registered substance. You have not provided any direct measurements of the toxicokinetics (and degradation) of the registered substance, and so your assertion of similarity in degradation represents speculation. ECHA notes that the *in vivo* data on the C8 analogue states that "*Only 2-ethylhexanol and a single isomer of mono-(2-ethylhexyl)trimellitate appear to be absorbed.*" ECHA concludes that there is systemic availability of non-common products, and that your argument of common degradation does not provide a basis which would predict the toxicological properties of the structurally different systemically available substances. Hence, the arguments of common degradation do not provide a robust basis for predicting the properties of the registered substance.

Additionally, ECHA has taken into account all of your arguments together, and notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across.

ECHA considers that this grouping and read-across approach does not provide a robust basis whereby the human health effects/ environmental effects / environmental fate may be predicted from data for reference substance(s) within the group, and hence does not comply

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework

with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5, and these are set out under the endpoint concerned.

In your comments to the draft decision, ECHA notes your agreement that the *"justification for the use of read-across and (Q)SAR in the registration dossier contained insufficient detail to permit ECHA to effectively assess whether the registration dossier complies with the requirements [...]"* and that you intend to update your read-across justification in your registration dossier taking into account the detailed ECHA guidance. Furthermore, you have argued that new data is being generated on one of the analogue substances (TM8), which will *"increase the pool of information potentially available for read-across purposes"*.

Therefore you suggested to wait for the outcome of the repeated dose toxicity (90-day) study on TM8, before the current decision is being issued.

ECHA draws your attention to the fact that a reliable prediction can only be based on a matrix-structured set of data, which gives confidence in the prediction proposed and thereby allows to bridge data gaps for a given property. In the current registration dossier ECHA notes that you have not provided any data points (e.g. on lower-tier endpoints) on the registered substance, which, in turn, does not allow you to compare (eco)toxicological properties and then rely on reliable and justifiable predictions.

Therefore, ECHA considers that the outcome of any study on the source substance alone will not be sufficient for you to address the deficiencies highlighted above. More specifically ECHA considers that, in the absence of any bridging study on the registered substance (eg. subacute or screening study), your read-across approach cannot be robustly supported.

ECHA also notes your intention, provided in your comments to the Member States' proposals for amendment (PfAs), to "*examine whether additional information from experimental data or modelling can enhance the argumentation in compliance with ECHA's guidance*". You indicated that the "*focus will be on* in silico *modelling which will be undertaken for the (eco)-toxicological endpoints of concern on both the target and source substances*". You are reminded that ECHA is only able to assess the viability, reliability and applicability of your information, once you have submitted it. ECHA will also assess its relevance for the toxicological endpoints of concern, on both the target and source substances. At the same time, ECHA notes that relying on training sets for some endpoints, especially for the higher tier ones, is unlikely to be sufficient to support your read-across approach and to allow you to predict the (eco)toxicological properties.

ECHA reminds you that it is your responsibility to update your dossier, including the read-across justification and supporting information, when new data becomes available, and that ECHA cannot delay the decision-making process to await that such data become available. ECHA notes that the deadline in the current decision may allow you to take into consideration the data generated on the analogue substance.
The read-across is not accepted due to the lack of documentation and justification on why the data gaps of the target substance can be predicted based on the data and properties of the surrogate substances.

0. 2. (Quantitative) Structure-Activity Relationship

Your registration dossier contains adaptation arguments in form of a application of quantitative structure activity relationship models ((Q)SARs) under Annex XI, Section 1.3. of the REACH Regulation, for the following endpoints:

- *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.)
- Hydrolysis as a function of pH (Annex VIII, 9.2.2.1.)
- Ready biodegradability (Annex VII, 9.2.1.1.)
- Bioaccumulation in aquatic species (Annex IX, 9.3.2.)

ECHA has considered first the scientific and regulatory validity of your approach in general before assessing the individual endpoints (sections 8, 12 and16 below).

You have proposed to adapt the information requirements of the substance, as listed above, by providing results obtained from the application of quantitative structure activity relationship models ((Q)SARs). According to Annex XI, Section 1.3. of the REACH Regulation the results of (Q)SARs may be used instead of testing when the following conditions are met:

- results are derived from a (Q)SAR model whose scientific validity has been established,
- the substance falls within the applicability domain of the (Q)SAR model,
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied model is provided.

For all the above-mentioned endpoints, you have used QSAR predictions for only the main constituent (i.e. [redacted], which has a typical concentration of [redacted]% according to the composition you reported) of the registered substance. You did not take into account other components nor provided any explanation on how these results can be extrapolated to the registered substance.

In addition, you did not provide the adequate and reliable documentation of the applied model referred to under the last bullet point. Without such documentation, ECHA is not in a position to assess whether the other conditions outlined in the first three bullet points are fulfilled. As you have not demonstrated that the conditions of the adaptation of Annex XI, Section 1.3. of the REACH Regulation are fulfilled, ECHA cannot accept the adaptation.

For the adaptation to be acceptable, you need to provide the above-mentioned documentation and you would have to demonstrate that the first three conditions for applying the proposed adaptation are fulfilled. The general form of the (Q)SAR Model Reporting Format (QMRF) and (Q)SAR Prediction Reporting Format (QPRF), are described in the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6: (Q)SARs and grouping of chemicals (ECHA, May 2008). Under REACH, reporting formats can be submitted to ECHA as attached files in an IUCLID dossier.

Finally, you stated that *"the trimellitate esters are expected to be stable against abiotic degradation and to be only slowly biodegradable through (Q)SAR estimations, do not suggest that biodegradation is feasible. Biodegradation rates may be limited due to poor water solubility of these substances"*. ECHA notes that (i) your dossier does not contain any measured degradation data, (ii) you did not provide QPRF and QMRF documentation to support your statement (*"validated (Q)SAR estimations"*), and (iii) your statement is in contradiction with another statement that you included in your justification to apply a read-across approach: *"common degradation – hydrolysis to the di-ester, then mono-ester then further hydrolysis to yield trimellitic acid and the corresponding alcohol - it is considered that*

the physico-chemical and (eco)toxicological properties of the substances in this category will be similar."
Therefore the prediction cannot be considered reliable or acceptable, and thus cannot be used to fulfil the endpoint requirement.

ECHA notes your agreement to review the validity of the models applied, as for the adaptation to be acceptable, it is necessary to provide the above-mentioned documentation to be able to demonstrate that the conditions for applying the proposed adaptation are fulfilled.

As the conditions for adapting the information requirements in accordance with Annex XI, Section 1.3. of the REACH Regulation have not been fulfilled, your respective adaptation argument is rejected.

ECHA notes your agreement to the existence of deficiencies in the dossier and your intent to update your documentation, especially with regards to the *"structural and mechanistic profiles of both the main constituent -* [redacted] *(CAS No.* [redacted]*, EC No.* [redacted]*) - together with the other seven main group constituents of the registered substance is necessary to form a reliable basis for the justification of the selection of the main constituent in the consideration of read-across and (Q)SAR studies", and to* the provision the (Q)SAR Model Reporting Format (QMRF) and (Q)SAR Prediction Reporting Format (QPRF), as described in Chapter R.6: (Q)SARs and grouping of chemicals of the ECHA Guidance.

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 as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records (OECD TG 471) with the following 3 analogue substances: one study with TM8 (Trioctyl benzene-1,2,4-tricarboxylate), one study with TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester) and two studies with TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate), having the following EC numbers 201-877-4, 290-754-9 / 268-007-3, and 222-020-0, respectively.

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected. In addition ECHA notes that the study with TM8-10, from 1987 (reliability 2) was tested in 3 strains only, which is not in accordance with the OECD TG 471. You acknowledged this finding in your comments on the draft decision.

Also you provided two QSAR tests from 2014 (EPA T.E.S.T/ QSAR Toolbox) on a constituent of the registered substance TM9: trinonyl benzene tricarboxylate. However you did not provide any justification as to why it is the most representative component, for the registered substance. However, as explained above in Appendix 1, section 0.2. of this decision, your adaptation of the information requirement is rejected. Hence ECHA considers that the information provided does not fulfil the endpoint requirement.

Based on the information provided on this endpoint for the registered substance in the technical dossier, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14/ OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14/ OECD TG 471).

2. 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 as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records (OECD TG 473) with the following 2 analogue substances: one study with TM8 (Trioctyl benzene-1,2,4-tricarboxylate), one study with TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester) and two studies with TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate), having the following EC numbers 201-877-4, 290-754-9 / 268-007-3, and 222-020-0, respectively. However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain appropriate study records for these information requirements. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to

meet this information requirement provided that both studies requested under points 1 and 2 of this decision have negative results.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records (OECD TG 476) with the following 2 analogue substances: one study with TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester) and two studies with TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate), having the following EC numbers 290-754-9 / 268-007-3, and 222-020-0, respectively. However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under points 1 and 2 have negative results.

4. 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 as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You provided several repeated dose toxicity studies on different analogue substances, on (a) TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate; EC number 222-020-0), (b) TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester; EC numbers 290-754-9 / 268-007-3) and (c) TM8 (Trioctyl benzene-1,2,4-tricarboxylate; EC number 201-877-4):

(a) a sub-chronic toxicity study (90-day) (OECD TG 408, 2012, GLP, rel. 2) tested with the TOTM substance, unchanged in the diet, was provided: it showed an increase in neutrophils and a decrease in spleen weight together with a slight reduction of grip strength as observed in the high dose animals of both sexes at the end of treatment. The reported NOAEL is 225 mg/kg/day, equivalent to the mid-dose (as reduction of grip strength was observed at the top dose).

Four subacute (28-day) studies were submitted with the same TOTM substance, two of which were not used for the assessment (reliability 3): One gavage study (OECD TG 407, 1996, GLP, rel. 2) tested with the TOTM substance in corn oil returned only negative results and histopathology on testis was not performed; the reported NOAEL is 1000 mg/kg/day for females and 100 mg/kg/day for males. One dietary study (non-guideline study, 1985, rel. 2) tested with the TOTM substance unchanged, with histopathology on testis, showed "*hepatic effects of TOTM - liver enlargement,*

increases in palmitoyl-CoA oxidation and the activities of catalase and carnitine acetyltransferase and the induction of slight peroxisome proliferation", in addition to haematological and clinical chemistry findings; the reported NOAEL is 184 mg/kg/day (low dose).

Finally one reproduction/ developmental screening gavage study (OECD TG 421, 1998, GLP, rel. 2) tested with the TOTM substance in corn oil showed no clinical signs or gross pathology findings in parent animals (the histopathology findings are discussed below, under request 5).

(b) A sub-chronic toxicity study (90-day) (OECD TG 408, 2014, GLP, rel. 2) tested with the TM8-10 substance, administered in corn oil by gavage was provided: it showed an increase of neutrophils (reversible after 4 weeks) and a slight reduction of grip strength. The reported NOAEL was 500 mg/kg/day, equivalent to the top dose as no effect was observed.

One gavage subacute (28-day) study (OECD TG 407, 2010, GLP, rel. 2) with the TM8-10 substance in corn oil was provided: it showed an increase in leucocytes and an increase of liver and adrenal weights (absolute and relative), completely reversible over a 2-week recovery period in the high dose (1000 mg/kg/day) animals. Only mild effects were observed in the animals (essentially males) dosed at 300 mg/kg/day, which was used as reported NOAEL.

(c) A gavage subacute (28-day) toxicity study (OECD TG 422, 2001, GLP, rel. 2) tested with the TM8 substance in corn oil, was provided, showing a decrease in white blood cells, and reduced testis weight in the mid-dose only; the reported NOAEL is 125 mg/kg/day for males and 30 mg/kg/day for females, because of the haematological findings.

ECHA reviewed the data provided and considers that the subacute toxicity and screening studies do not fulfil the requirements of Annex IX, Section 8.6.2, because of their reduced study length and/ or reduced sensitivity (lower number of animals) as compared to the OECD TG 408 for a 90-day subchronic toxicity study.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing several study records for a sub-chronic toxicity study (90-day) (OECD TG 408) with two analogue substances (TOTM and TM8-10), and a subacute toxicity study on a third analogue substance (TM8).

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.

Notwithstanding the rejection of the read-across, ECHA still reviewed the merits of the subchronic study on TM8-10 you have submitted, as follows: the subchronic study on TM8-10 does not fulfill the requirements of Annex IX, Section 8.6.2 because it is not compliant with the OECD TG 408, and specifically para 13-16, which states that *"Unless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering."* No adverse effect was observed at the top dose of 500 mg/kg/day, there is no basis given for believing that this dose would induce toxicity, and the dose used is less than the limit dose of 1000 mg/kg/day.

You have commented and have provided a rationale for the dose selection in the sub-chronic toxicity study (90-day) (OECD TG 408, 2014, GLP) on the TM8-10 substance, as *"based on findings from a sub-acute study (28-day) which found (minor) effects at 1000 mg/kg/day." These effects were expected to become significant when the exposure period was extended to 90-days at this dose level. As a result, and mindful of the need to minimise pain and distress to experimental animals, a lower dose level of 500 mg/kg/day was selected for the sub-chronic study criticised by ECHA".*

However, minor effects in a 28-day study do not always result in effects in a sub-chronic (90-day) study. The actual results of the study you provided demonstrated this eventuality. Therefore the criteria of the OECD TG 408 remains not being met. In conclusion, the study does not fulfil the requirement of Annex IX, Section 8.6.2., firstly because the read-across to TM8-10 is rejected, and secondly because the study on TM8-10 is not compliant with the scientific requirements of the OECD TG 408.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration.

More specifically, the substance is a liquid of very low vapour pressure. Uses with industrial, professional, consumers and some spray application, with low concentration are reported in the chemical safety report. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

Notes for your consideration

The mode of administration by gavage using corn oil is believed to have an impact on whether the effects under discussion (reduced testis weight, increase adrenals weight ...) are observed. ECHA considers that the vehicle may influence the absorption of the substance TOTM in the organism, by increasing its bioavailability triggering the endocrine disrupting–related effects at equivalent dose levels.

Therefore the study should preferably be performed by gavage using corn oil as a vehicle.

In addition to better assess whether similar relevant mode(s) of actions relevant to endocrine disruption could be occurring, the use of corn oil/ gavage administration would allow to better compare the effects among analogue substances: two of the subacute toxicity studies (OECD TG 407/1996 and OECD TG 421/1998), with TOTM were performed by gavage/ in corn oil, as well in the other repeated dose toxicity studies with TM8-10 (90-day) and TM8 (28-day).

Finally ECHA draws your attention to the study design you will decide upon, since the sub-chronic toxicity study may provide information on effects that is relevant for triggers in the

extend one generation reproductive toxicity study (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

5. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You provided two screening studies for reproductive/ developmental toxicity on two analogue substances, namely TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate, EC number 222-020-0) and TM8 (Trioctyl benzene-1,2,4-tricarboxylate; EC number 201-877-4); both with reliability 2:

- a Reproduction/ Developmental Toxicity Screening Test (OECD TG 421, 1998, GLP) tested with the TOTM substance, in corn oil by gavage, showed "*slightly reduced numbers of spermatocytes & spermatids in 2/12 & 11/12 animals given 300 & 1000 mg/kg/day TOTM respectively and a moderate decrease in 1/12 animals given 1000 mg/kg/day TOTM. In addition the number of cells/number of spermatids in seminiferous tubules was reduced in males given 300 mg/kg/day TOTM in stages I-VI. In males given 1000 mg/kg/day in stage I-IV numbers of spermatocytes &spermatids were reduced. In stages VII-XIV spermatocyte & spermatid numbers continued to be low & the Sertoli cell ratio was also reduced.*

- a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD TG 422, 2001, GLP) tested with the TM8 substance, in corn oil by gavage, showed an *decrease in white blood cells, and a testis weight reduced in the mid-dose only .*

ECHA considers that the provided screening studies for reproductive/ developmental toxicity do not fulfil the requirements of the OECD TG 443, since, these studies do not provide the information required by Annex X, Section 8.7.3. because they do not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. In addition, the criteria for extension of the Cohort 1B are met for the registered substance according to column 2 of Annex X, Section 8.7.3., because there are indications of endocrine disruptor mode of action (see below), and the information for this property is missing. You have not provided any study record of an

extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement. While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

You have provided the following justification for the [weight of evidence] adaptation: "*This substance is manufactured by the registrant in quantities >1000 tpa. As such, a two-generation reproductive toxicity study is required in accordance with REACH Regulation 1907/2006, Annex X, Section 8.7.3 of Column 1, Annex IX. It is proposed to waive the need to conduct this study on the basis of the fact that well-conducted OECD 421 reproductive/ developmental toxicity screening studies and data from subchronic repeat dose toxicity studies show no functional effect on the reproductive performance of both male and female rats. [...] Furthermore, it is possible that, for this class of substance, by association with phthalate esters, the principle reproductive toxicity potential is towards the developing male testes. [...]*".

To support your weight of evidence adaptation, you have provided the following sources of information:

- OECD TG 408 study (2012), rat, with the analogue substance TOTM, unchanged in the diet
- OECD TG 408 study (2014), rat, with the analogue substance TM8-10, in corn oil by gavage
- OECD TG 421 study (1998), rat, oral route, with the analogue substance TOTM, in corn oil by gavage
- OECD TG 422 study (2001), rat, oral route, with the analogue substance TM8, in corn oil by gavage

Based on the results of these studies you proposed that these would "*provide adequate data to demonstrate the potential toxicity to reproduction of the substance to humans and to derive relevant DNELs for oral exposure*". Furthermore, you state that "*for this class of substance, the principle reproductive toxicity potential is towards the developing male testes. This aspect of the toxicological profile has been studied adequately using RNA transcriptional profiling in an assay that subscribes to the principle of the 3R's*".

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation. Therefore, your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision.

ECHA considers that the OECD TG 443 study provides, in addition to information to general toxicity, information on two aspects in particular, namely on sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and post-natal and adult exposures in the F1 generation and F2 generation until weaning (further referred to as 'effects on offspring').
Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition,

and lactation) in the P0 and F1 parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P0 and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect endocrine disruptive properties, postnatal development of F2 generation. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' need to be considered.
Furthermore, for an adaptation pursuant to Annex XI, Section 1.2. to be accepted, the relative values/ weights of different pieces of the provided information need to be assessed as indicated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.4.4. In particular relevance, reliability and adequacy for the purpose as well as consistency of results/data need to be considered.

In view of the above, ECHA emphasises that the information from the provided OECD TG 408, 421 and 422 studies are not sufficient to address the information requirement of an extended one-generation reproductive toxicity study because these studies do not include key parameters such as 'sexual function and fertility' (especially for the F1), 'effects on offspring' (particularly after weaning and for the F2 generation) or sufficient statistical power (animal numbers).

Moreover, ECHA notes that your assumption that these studies would "*provide adequate data to demonstrate the potential toxicity to reproduction of the substance to humans and to derive relevant DNELs for oral exposure*" is not supported by any documentation or evidence. Furthermore, this consideration relates to risk assessment/ characterisation rather than addressing the potential hazardous properties of the registered substance, i.e. addressing the missing elements of the requested extended one-generataion reproductive toxicity study. Your statement does therefore not address the question whether the substance has or has not a dangerous (hazardous) property with respect to reproductive toxicity as required by the requested extended one-generation reproductive toxicity study.

Finally, you state that "*for this class of substance, the principle reproductive toxicity potential is towards the developing male testes. This aspect of the toxicological profile has been studied adequately using RNA transcriptional profiling in an assay that subscribes to the principle of the 3R's.*" Your study on toxicogenomic analysis of genes associated with phthalate-induced testicular dysgenesis at best claims to detect genes associated with phthalate-induced testicular dysgenesis, and merely excludes this particular mechanism of action for this particular defect. ECHA is of the opinion that the occurrence of other relevant effects cannot be excluded on the basis of this study.
Therefore this statement does not satisfactorily address the question whether the substance has or has not a dangerous (hazardous) property with respect to reproductive toxicity as required by the requested extended one-generation reproductive toxicity study.

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume or conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

In addition, ECHA notes that the provided four studies have been performed with analogue substances (TOTM, TM8-10 and TM8). Since the read-across approach for those studies is rejected (as per Appendix 1, section 0.1 above), this information cannot be used as reliable source of information within a weight of evidence adaptation.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

In your comments, you argued several points of the above, such as the use of two screening studies on the source substances TM8 and TOTM, the conclusion of the SEv process on TOTM, and the use of toxicogenomic analysis of genes. You made comment on two screening studies on the source substances TM8 and TOTM, which did not establish that the information requirement is met. As the read-across approach used is rejected, ECHA has merely discussed the merit of the individual studies in terms of whether these studies fulfil the information requirements of Annex X, section 8.7.3. (as possibly adapted via Annex XI, Sections 1.2 and 1.5).

ECHA notes that the Substance Evaluation and compliance check are different processes. Substance Evaluation investigates and may resolve particular concerns, but the conclusion of substance evaluation on TOTM does not mean that the dossier for the registered substance is compliant with the REACH information requirements.

You suggested a re-wording of the summary of the toxicogenomic study. ECHA points out that this would not establish that the information requirement is met, as ECHA merely assessed the merit of the toxicogenomic analysis of genes associated with phthalate-induced testicular dysgenesis, to fulfil the information requirements of Annex X, section 8.7.3. (as adapted via Annex XI, section 1.2 and 1.5).

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of the study design of the required study.

b) The specifications for the study design

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study performed with the registered substance in corn oil administered by gavage, shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to finally decide on the study design of the extended one-generation reproductive toxicity study following the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).
The sub-chronic toxicity study may provide information on effects that are relevant for triggers: namely weight changes and histopathological observations of organs may be indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts.

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). As supported by the hydrophobicity of the substance (Log K_{ow} calculated is 13.54), ECHA considers that ten weeks exposure duration will allow to ensure that the steady state in parental animals has been reached before mating. In addition, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection of registered substance should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that you conduct a dose range-finding study (or range finding studies) and that you report the results thereof with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

The extension is *inter alia* required, if "*the use of the registered substance is leading to significant exposure of consumers and professionals*" (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X), and "*there are indications that the internal dose for the registered substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure*" (column 2, first paragraph, lit. (b), second indent of section 8.7.3., Annex X) *or "there are indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches"* (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex X).

The first trigger is met (lit. (a)), since the use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by professionals as lubricants and lubricant additives (e.g. PROCs 4, 8a, 8b, 9, 10, 11, 13, 17, 18) and consumers as lubricants (PC24) and polymers (PC32).

A second trigger (lit. (b) 2nd) is met since there are indications, due to the calculated high logK_{ow} value (logK_{ow}= 13.54), that the internal dose for the substance will reach the steady-state after an extended exposure . In your comments to the draft decision, you indicated that you will perform experimental measurements of log K_{ow} on the registered substance or its constituents.

One member state questions whether, with such a high log K_{ow} , the substance is likely to reach the systemic circulation and has proposed to generate data to assess whether the registered substance is absorbed through the gut wall. During the MSC-meeting you indicated that you plan to investigate absorption using an *in vitro* model such as the Caco-2

permeability assay. However you also noted that, although the assay is well-established, there may be practical difficulties due to the UVCB nature of the registered substance.

Nonetheless ECHA notes that currently there is no evidence to dismiss absorption of the registered substance based on effects observed after repeated dose treatments with various analogues.

ECHA considers that, with the data currently available in your dossier, the second trigger (lit. (b) 2nd) is met (ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 - version 6.0, July 2017).

ECHA also considers that another trigger (lit. (b) 3rd) is met as there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies. Specifically the reproduction/ developmental toxicity screening study (OECD TG 421) on the analogue substance TOTM gives indications of one or more modes of action related to endocrine disruption, because effects on spermatocytes and spermatids are observed (see above). Therefore, notwithstanding the rejection of the read-across adaptation, this feature meets the toxicity criteria (lit. (b) 3rd).

Also you have stated that the registered substance is part of a "*class of substance, [where] the principle reproductive toxicity potential is towards the developing male testis.*" These testis effects are an indication of endocrine-disrupting modes of action.

In your comments to the draft decision, you argued that: (1) the decision making process of an analogue substance (TM8) led to a different study design. and (2) that the conclusion of the substance evaluation on TOTM, regarding the reproductive properties not requiring further testing to fulfil the PBT criteria under review, is not consistent with the triggering of Cohort 1B in this decision.

ECHA first notes that a different study design was justified by different *in vivo* studies during the previous assessment for TM8. Secondly, there are are no inconsistencies across the various decisions taken on structurally similar substances, since the substance evaluation was merely focusing on the PBT criteria and not on the compliance with the reproductive toxicity endpoint under REACH.

In your comments you also argued that toxicogenomics analysis of genes demonstrated that the analogues do not exert endocrine disrupting properties. ECHA considers that the conclusion of these *in vitro* assays merely concluded on TOTM and TM8-10 analogues substances are "*unlikely to cause testicular dysgenesis in rats under the treatment conditions*", as do the positive controls DEHP and MEHP administered at the same dose level (500 mg/kg)

You also commented that the results of the sub chronic study (OECD TG 408) on TOTM are not consistent with the results from the screening reproductive/ development study (OECD TG 421) on the same analogue subtance. However ECHA considers that there are no inconsistencies across the two studies, the gavage screening reproductive/ development study (OECD TG 421) and the dietary sub chronic study (OECD TG 408), based on the the vehicle effect, leading to a different level of absorption in the digestive tract and resulting in different effects obtained with the TOTM analogue substance. Consequently the absence of histopathological effects in testis in the dietary sub-chronic study (OECD TG 408, 2012) cannot be considered as contradictory to the findings of the gavage/ corn oil screening study (OECD TG 421, 1998).

Finally ECHA concludes that with the data currently available, the trigger (lit. (b) 3rd) is met.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure, and there are indications of modes of action related to endocrine disruption.

One member state has proposed to amend the decision, by deleting the extension of the Cohort 1B. ECHA notes your comment to the PfA, where you indicated that you "*prefer that data from such a study on the registered substance itself be available before making a decision on the necessity to extend the EOGRTS with additional cohorts.*" However as described above, the triggers are already met which results in triggering the extension of Cohort 1B. ECHA will evaluate the 90-day study sequentially to see if there are any changes needed for th study design.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection and mode of administration

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

By analogy to the request under point 4., and to enhance absorption in the digestive tract, the study should be performed preferably by gavage using corn oil as a vehicle.

c) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.

Currently, the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) is not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 4) and/or any other relevant information (such as bioaccumulation as per request 16) may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) on the registered substance is to be conducted first and the study results submitted to ECHA in a dossier update by ***3 January 2019***. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **25 March 2019** (i.e. within three

months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by ***25 March 2019***, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision ***25 June 2021***.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (*version 6.0, July 2017*)*).

ECHA draws your attention that providing the information relevant to bioaccumulation potential (eg. Bioaccumulation assay, as per request 16, Caco-2 permeability assay,...) simutaneously with the results of the repeated dose toxicity (90-day) study would allow to take an informed decision on whether changes in the study design are needed. Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/ non-existence of the conditions/ triggers must be documented.

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records for a pre-natal developmental toxicity study (OECD TG 414), in rats: one study with TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester) and one with TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate), having the following EC numbers 290-754-9 / 268-007-3, and 222-020-0, respectively.

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.

Therefore, your adaptation of the information requirement is rejected.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. Based on this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid of very low vapour pressure (2.96E-05 Pa), ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the analogue substances (key study) TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester; EC number 290-754-9 / 268-007-3) and another pre-natal developmental toxicity study in rats (labelled "weight of evidence") with TOTM (or TEHTM; Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate; EC number 222-020-0). You clarified in your comments that both studies were submitted as "weight of evidence" information to meet the information requirement.

As explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement by way of read-across is rejected. Therefore the two studies, individually, fail to meet the information requirement for a pre-natal developmental toxicity study on the registered substance.

Moreover you have claimed an adaptation according to Annex XI, Section 1.2., using weight of evidence, but providing no justification for weight of evidence. An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation.

Also having regard to your comment that you do not accept "*that reasoning to explain why the second species information requirement would be covered is not present in the examined registration dossier*", ECHA takes the following overall conclusions:
(i) you have not provided any reasoning to explain how the two studies performed in rats, on analogue substances (TOTM and TM8-10), can be used as part of a "weight of evidence" adaptation.
(ii) Consequently, you have not provided "adequate and reliable documentation", as required by Annex XI, Section 1.1.2.;
(iii) you have not provided information for a pre-natal developmental toxicity study in a second species other than rats, nor any reasoning to explain why the second species information requirement would be covered;

(iv) as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement by way of read-across is rejected. Accordingly, ECHA considers that the provided studies are not relevant for the registered substance.

For all the above reasons, ECHA considers that there is not sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement of prenatal developmental toxicity in a second species (Annex X, 8.7.2), and so the requirements of Annex XI, Section 1.2 are not met. Therefore, your adaptation of the information requirement is rejected.

In your comments you also pointed to (i) inconsistencies in ECHA's conclusions "*with respect to pre-natal developmental toxicity the data provided on TOTM is not relevant for the registered substance, while for the extended one-generation reproductive toxicity study, the data provided on TOTM are cited as a key indicator for requiring adaptation of the standard testing requirement".*

ECHA notes that there is no inconsistency but there is a need to clarify the difference between an acceptable grouping and read-across (Annex XI, section 1.5) and a concern based upon a structurally analogous substance (Annex X, section 8.7.3).

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. Based on this default assumption, ECHA considers that the test should be performed with rabbit as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

8. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The technical dossier does not contain relevant data to fulfil this standard information requirement. While you have not explicitly claimed an adaptation, you have provided information in the form of two predictions calculated with the SPARC and HYDROWIN models, which could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.3., using (Q)SAR predictions. However, ECHA as explained above in Appendix 1, section 0.2. of this decision, your adaptation of the information requirement, according to Annex XI, Section 1.3. is rejected.

Furthermore, according to your prediction performed at 2 pH values, you concluded that the half-lives are 2.15 years at pH 7 and 78.4 days at pH 8. According to the test guidelines EU C.7 and OECD TG 111 "*The hydrolysis test should be performed at pH values of 4, 7 and 9*". As the information reported in the technical dossier does not contain results of hydrolysis in all three pH values prescribed by the method, it is not adequate to fulfil the standard information requirement.

In addition, you used hydrolysis information as a read-across argument. However as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected. Finally, given the contradictions in the read across argumentation, a test seems necessary to conclude on this issue.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Therefore, you are requested to submit the information for this endpoint using an appropriate test method on the registered substance.

Based on your comment that ECHA confuses a statement on hydrolysis and one on metabolism, ECHA would like to reemphasize that the hydrolysis waiving was not to be confused with the read-across justification about hydrolysis of the trimellitate esters into common degradation products. This term was used under the toxicokinetic and metabolism considerations which are not to be mixed with hydrolysis applied under abiotic degradation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Hydrolysis as a function of pH (test method: EU C.7/ OECD TG 111).

9. Activated Sludge, Respiration Inhibition Testing (Annex VIII, Section 9.1.4.)

"Activated sludge respiration inhibition testing" is a standard information requirement as laid down in Annex VIII, Section 9.1.4. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records (OECD TG 209 and a non TG Hüls Methode) with the following 2 analogue substances: TOTM (1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester; EC number 222-020-0) and TM8-10 (1,2,4-Benzenetricarboxylic acid,

mixed decyl and octyl triesters/ 1,2,4-Benzenetricarboxylic acid, decyl octyl ester; EC numbers 290-754-9 / 268-007-3).

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.

In addition the test substance is reported to have high logK_{ow} (13.54) and extremely low water solubility (0.000081 µg/L), based on extrapolation from the main constituent (i.e. [redacted]) which has a typical concentration of [redacted]% according to the composition you reported. ECHA notes that the reliability of the prediction is questionable because the Log K_{ow} of the substance is outside of range of the training set compounds. As explained in Appendix 1, section 0.2. of this decision, the actual LogK_{ow} and water solubility of the test substance are uncertain. Therefore there is no ground to conclude on the validity of the adaptation of column 2 of Annex VIII, Section 9.1.4.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) activated sludge respiration inhibition test (carbon and ammonium oxidation) (test method OECD TG 209) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.4.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Activated sludge, respiration inhibition test (carbon and ammonium oxidation) (test method: OECD TG 209).

10. 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 as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing 4 study records for the long term aquatic invertebrates test on Daphnia respectively with the analogue substances TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester; EC numbers 290-754-9 / 268-007-3), TM8 (Trioctyl benzene-1,2,4-tricarboxylate; EC number 201-877-4) and TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate; EC number 222-020-0), as per OECD TG 211, old 202 second part and OECD TG 211 plus a non TG from FIFRA registration of pesticides in USA(ASTM/EPA method 29696-29741) for the analogue TOTM.

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement cannot be accepted.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Furthermore, notwithstanding the rejection of the read-across adaptation, ECHA notes that the analogues in question raise a concern for a potential endocrine-disrupting mode of action for the environment as well. For these analogues, findings of endocrine disrupting effects for anti-androgenic effects were detected. In particular, as per the test results from an OECD TG 422 rat study on the analogue, TM8 (GLP, 2001) the following findings were described as anti-androgenic effects: the testis weight of males treated at 125 mg/kg/day was statistically significantly reduced although no dose-related trend was apparent.
Besides this endocrine-disrupting effect, atrophy of seminiferous tubules was observed in the control treatment groups (30, 125 and 500 mg/kg/day). In the epididymis, cell debris in the lumen and reduced epididymal sperm were observed in single animals of the control group and groups treated at 30 and 500 mg/kg/day. The animal treated at 500 mg/kg/day also exhibited spermatic granuloma. Interstitial lymphocytic infiltration was observed in control animals and in those treated at 30, 125 and 500 mg/kg/day.
Cellular infiltration of lymphocytes and plasma cells was observed in the interstitium/ epithelium of the prostate of two animals treated at 500 mg/kg/day and four control animals. No ovarian abnormalities were observed in females.

Furthermore as outlined also under request 5 above:

(i) You listed that an OECD screening study of reproductive toxicity on another trimellitate (TOTM), revealed no functional changes in fertility or reproductive performance, although histopathological examination revealed reduced spermatocytes & spermatids in the testes of males given the substance at doses of 300 and 1000 mg/kg/day. These testicular effects were not apparent in the screening study above despite the exposure period being approximately double that of the screening study;
(ii) Some of the analogous phthalate esters are known to be reproductive toxicants, targeting the developing male testes, and this aspect of the toxicological profile has been studied adequately using RNA transcriptional profiling in assays on two substances, 1,2,4 -Benzenetricarboxylic acid, decyl octyl ester and TOTM. The outcome of these studies indicate that the substances do not cause repression of genes in the testicular mal-development pathway indicating that they are unlikely to cause testicular dysgenesis in rats as is seen with some phthalate esters. These studies however have to be applied to the environment and the potential effects on Fish cannot be concluded from rats and *in vitro* studies.

ECHA also notes that MEHP, for which the question of the potential endocrine disruption properties is under investigation, is described as a common metabolite of TOTM and Diplast TM9.

Therefore, and as part of the OECD TG 211 parameters (listed in section 44, version 2013), you are required to monitor, in addition to the apical parameters, the sex-ratio (e.g record the presence of male neonates or of ephippia, and record possibly intrinsic rate of population increase) when performing the long term toxicity test to Daphnia.

ECHA takes note of your comments with regard to the proof that MEHP is not a degradation products of TOTM nor of TM8.
Nevertheless, and with regard to both the rejection of the read-across as with the multiple uses and exposure of environmental organisms and data gap for long-term aquatic organisms, ECHA considers that the potential concerns on endocrine disruptions for

invertebrates and vertebrates remains. ECHA further notes that this additional requested parameter is listed in paragraph 44 of the test guideline 211 as mentioned in the draft decision.

ECHA considers that this sex ratio parameter might be used for evaluation of endocrine disruption potential of a substance. Since there is a concern about endocrine disruption potential of the substance ECHA considers that this parameter is relevant and such parameter is not disproportionate nor beyond REACH information requirements.
Therefore, the request for an OECD TG 211 will remain including the sex ratio or counting of ephippia, if any is generated during the test. This parameter is part of the test guideline parameters and does not require extra testing. With regard to the absence of long-term aquatic toxicity data on both invertebrates and Fish, this parameter is not considered as disproportionate and will help you to clarify if there are potential disrupting properties of the registered substance or not as you do claim for your registered substance or its constituents.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211, inlcuding sex-ratio parameter).

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

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record (OECD TG 204) with the following analogue substance: TOTM (Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate; EC number 222-020-0). You further justifed that there is a lack of chronic toxicity on Daphnia, although the substance is poorly soluble (Annex VII, column 2 requirement).

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement is rejected.
Furthermore, ECHA notes that the OECD TG 204 has been invalidated as of 2 April 2014. Hence, even if the read-across adaptation would be accepted, this study cannot be used to fulfil the information requirement for this endpoint.

Therefore, ECHA concludes that your attempts to adapt the information requirement cannot be accepted.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215)

are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

Note that the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth (see ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b, Figure R.7.8-4).

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA Guidance Chapter R7b, version 4.0, June 2017).

Testing alternative

The Fish Sexual Development Test (OECD TG 234) is also an appropriate test to cover the information requirement of Annex IX, Section 9.1.6. According to OECD TG 234, this test can be considered as "*an enhancement of TG 210: Fish, Early Life Stage Toxicity Test, where the exposure is continued until the fish are sexually differentiated,* [...]*, and endocrine-sensitive endpoints are added*".

For the same reasons outlined under request 10, above, ECHA considers that the Fish Sexual Development Test would be adequate to cover the information requirement and potential Endocrine disrupting (ED) properties. It would furthermore contribute to reduce the number of tests required, to be carried out, in order to fill in the current data gap and to address the ED concerns.

ECHA takes note of your comments and rejection to perform either specific parameters or test guideline applicable to the evaluation of endocrine disruptor properties. ECHA also acknowledged, as explained above, the proof that MEHP is not a degradation products of TOTM nor of TM8, based on an ongoing simulation degradation test on the sediment for one of the source substances used in the read-across argumentation.
Nevertheless and with regard to both the rejection of the read-across, as with the multiple uses and exposure of environmental organisms and data gap for long-term aquatic organisms, ECHA considers that the potential concerns on endocrine disruptions for invertebrates and vertebrates remains.

Therefore the request for an OECD TG 210 or for a choice to perform and OECD TG 234 will remain for you, in order to clarify if there are or not potential endocrine disrupting properties for the registered substance and not any of the read-across ones, e.g. TOTM. With regard to the absence of long-term aquatic toxicity data on both invertebrates and Fish, the endpoint request is maintained as is the concern about aquatic toxicity and other mode of action.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210), or
Fish Sexual Development Test (test method: OECD TG 234).

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.
Due to the low solubility of the substance in water, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

12. Ready biodegradability (Annex VII, Section 9.2.1.1.)

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, the endpoint 'ready biodegradability' (Annex VII, 9.2.1.1.) is a standard information requirement for registration for a substance produced or imported in quantities of 1 000 tonnes or more per year.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. and section 1.3 of the REACH Regulation by providing study records for one OECD TG 301 C and two OECD TG 301 B, performed with the following analogue substance TM8-10 (1,2,4-Benzenetricarboxylic acid, mixed decyl and octyl triesters / 1,2,4-Benzenetricarboxylic acid, decyl octyl ester; EC numbers 290-754-9 / 268-007-3).

However, as explained above in Appendix 1, section 0.1. of this decision, your adaptation of the information requirement cannot be accepted.

> You also provided a QSAR result for ready biodegradation using BIOWIN software on only the main constituent [redacted] of your registered substance.

However, as explained above in Appendix 1, section 0.2. of this decision, your adaptation of the information requirement cannot be accepted.
Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

In the present dossier, ECHA considers that the information on this endpoint is not adequate to conclude on ready biodegradability. The technical dossier does not either contain acceptable adaptation in accordance with Column 2 of Section 9.2.1.1 of Annex VII or Annex XI of the REACH Regulation for this standard information requirement.

ECHA acknowledges your agreement with regard to this information request and you proposal to perform either an OECD 301 B or 301 D prior to further testing of persistence or degradation of the registered substance in soil or/and sediment.
In your comments, you refer to enhanced ready biodegradation test, but the type of enhancement is not specified. There are a number of potential enhancements to the ready biodegradation test. These enhancements are applicable for the determination of persistence in vPvB/PBT assessment only but are not to be used for Classification and Labelling and quantitative exposure and risk assessment. Test substances that degrade in these enhanced biodegradation screening tests must not be considered readily biodegradable (unless ready biodegradability in a standard, i.e. without enhancements, ready biodegradation test is shown). Taking into account the above, ECHA considers that the acceptable enhancements are prolonged test duration and testing in larger test vessel.

Regarding the test method, Article 13(3) of the REACH Regulation states that "*Where tests on substance are required to generate information on intrinsic properties of substances, they shall be concluded in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission of the Agency as being appropriate*". In the present case, depending on the substance profile, the Registrant may conclude on ready biodegradability, by applying the most appropriate and suitable Test Guideline among those listed in the ECHA Guidance on information requirements and chemical safety assessment, Volume 5 Chapter R7b (June 2017) and in the paragraph below. The test guidelines include the description of their applicability domain.

ECHA agrees that ready biodegradation tests OECD 301 B or OECD 301 D would be suitable for testing poorly water soluble substances along with the OECD TG 301C and 301F.

In any case, ECHA considers that the OECD TG 310 may be the best option to test the ready biodegradability of the registered substance, as it is considered applicable also for soluble substances.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to perform one of the following tests with the registered substance subject to the present decision:

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: CO2 evolution test, OECD TG 301B),

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: MITI test (I), OECD TG 301C)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Closed bottle test, OECD TG 301D)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Manometric respirometry test, OECD TG 301F)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Ready biodegradability – CO2 in sealed vessels (headspace test), OECD TG 310) with the registered substance

13. Soil simulation testing (Annex IX, Section 9.2.1.3.)

"Soil simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.3. of the REACH Regulation for substances with a high potential for adsorption to soil.

You have sought to adapt this information requirement according to Annex IX, Section 9.2., column 2, Annex IX, Section 9.2.1.3., by providing the following justification for the adaptation: *"In accordance with REACH Regulation 1907/2006/EC (Annex IX - 9.2.1.2 & 9.2.1.4 - column 2), simulation tests of biodegradation in water and sediment do not need to be conducted as the substance can be regarded as biodegradable."*

According to Annex IX, Section 9.2.1.3, column 2 of the REACH Regulation, simulation testing on soil does not need to be conducted if the substance is readily biodegradable or if direct or

indirect exposure of soil is unlikely. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable as indicated in the section 12 above.
Furthermore, based on the uses reported in the technical dossier, ECHA considers that such uses are reported for which soil exposure cannot be excluded e.g. Environmental Release Category (ERC) 9b: 'Wide dispersive outdoor use of substances in closed systems and 10a: 'Wide dispersive outdoor use of long-life articles and materials with low release, as well as professional as consumer uses products PC24 (lubricants). ECHA therefore considers that you have not demonstrated that soil exposure is unlikely.

Therefore, your adaptation of the information requirement cannot be accepted.
ECHA notes also that you have not provided adequate justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to investigate further the degradation of the substance and its degradation products. In addition, the limited information you provided on Log K_{ow} is anyway indicative of high adsorptive properties.

On the basis of the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

In your comments, that are applicable to this request and the subsequent one, you stated that subsequent testing after the ready biodegradability test should address the compartment of concern. ECHA notes that PBT assessment should cover all environmental compartments. If the information on one simulation test can be used to conclude the persistence assessment for the remaining compartments, no further testing is needed.
The extrapolation between environmental compartments, if provided, should be accompanied with solid scientific justification.

ECHA agrees with your comment that OECD TG 309 if technically feasible should be conducted as a first study. In this case, the registered substance, or at least the water solubility provided for its main constituent, shows that it is highly insoluble and therefore ECHA considers that the OECD 309 is not technically feasible.
You are concerned that requested OECD 307 and OECD 308 studies should be performed both in aerobic and anaerobic conditions, and would be more difficult or worst case conditions for Persistence. The OECD TGs 307 and 308 allow testing both in anaerobic and aerobic conditions. However, ECHA notes that both requested studies are to be performed in aerobic conditions and strictly anaerobic testing is not requested in this decision. Therefore, ECHA did not modify the requests on the simulation testing.
Finally, ECHA would like to remind you that in deciding which information is required on persistence, bioaccumulation or toxicity in order to arrive at an unequivocal conclusion, care must be taken to avoid vertebrate animal testing when possible. This implies that, when for several properties further information is needed, the assessment should normally focus on clarifying the potential for persistence first. When it is clear that the P criterion is fulfilled, a stepwise approach should be followed to elucidate whether the B criterion is fulfilled, eventually followed by toxicity testing to clarify the T criterion.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Aerobic and anaerobic transformation in soil (test method EU C.23. / OECD TG 307) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.3.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with

Annex XIII of REACH Regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b (version 4.0, June 2017) specifies that simulation tests "attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3.0 February 2016) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 307. Therefore, the test should be performed at the temperature of 12°C.

Simulation tests performed in sediment or in soil possibly imply the formation of non-extractable residues (NER). These residues (of the parent substance and/or transformation products) are bound to the soil or to the sediment particles. NERs may potentially be re-mobilised as parent substance or transformation product unless they are irreversibly bound by covalent bonds or incorporated into the biomass. The amount and kind of NER is operationally defined by the extraction method employed. Strong extractions methods, for example soxhlet-extraction with apolar solvents, should be used in order to qualify the remaining NER as irreversibly bound residues. You are therefore requested to justify scientifically that the extraction method you will apply is appropriate to identify non-extractable residues (NER) as residues irreversibility bound to the soil.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in soil (test method: EU C.23./OECD TG 307). ECHA notes that you shall provide information, in order to cover the registered substance, including all relevant constituents, impurities and additives present in concentration of ≥ 0.1% (w/w). Alternatively, you shall provide a justification for why you consider certain constituents, impurities or additives present in concentration of ≥ 0.1% (w/w) or certain constituent fractions/blocks as not relevant for the PBT/vPvB assessment.

Notes for your consideration

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the test detailed above are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

14. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

"Sediment simulation testing" is a standard information requirement as laid down in Annex IX, section 9.2.1.4. of the REACH Regulation for substances with a high potential for adsorption to sediment.

You have sought to adapt this information requirement by providing the same justification that you provided for the simulation test in soil, above. Therefore, for the same reasons outlined in the simulation test in soil, your adaptation cannot be accepted. Furthermore, on the basis of the same considerations outlined under request 13, ECHA considers that there is a concern for this endpoint and that testing is thus required.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) Aerobic and anaerobic transformation in aquatic sediment systems (test method EU C.24. / OECD TG 308) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.4.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of REACH Regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "the information used for the purposes of assessment of the PBT/ vPvB properties shall be based on data obtained under relevant conditions". The Guidance on information requirements and chemical safety assessment R.7b (version 4.0, June 2017) specifies that simulation tests "*attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids [...], and a typical temperature that represents the particular environment*". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3.0 February 2016) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment.

Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 308. Therefore, the test should be performed at the temperature of 12°C.

Simulation tests performed in sediment or in soil possibly imply the formation of non-extractable residues (NER). These residues (of the parent substance and/or transformation products) are bound to the soil or to the sediment particles. NERs may potentially be re-mobilised as parent substance or transformation product unless they are irreversibly bound by covalent bonds or incorporated into the biomass. The amount and kind of NER is operationally defined by the extraction method employed. Strong extractions methods, for example soxhlet-extraction with apolar solvents, should be used in order to qualify the remaining NER as irreversibly bound residues. You are therefore requested to justify scientifically that the extraction method you will apply is appropriate to identify non-extractable residues (NER) as residues irreversibility bound to the sediment.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Aerobic and anaerobic transformation in aquatic sediment systems (test method: EU C.24./OECD TG 308).

Notes for your consideration

Before conducting the requested test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 (version 4.0, June 2017) and Chapter R.11, Section R.11.4.1.1 (version 3.0, June 2017) on PBT assessment [to determine the sequence in which the simulation tests are to be conducted and the necessity to conduct all of them. The order in which the simulation biodegradation tests are performed needs to take into account the intrinsic properties of the registered substance and the identified use and release patterns which could significantly influence the environmental fate of the registered substance.

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the test detailed above are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

15. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The biodegradation section in the technical dossier does not contain any information in relation to the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement. "

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable as also discussed in the sections 12, 13 and 14 above.

Furthermore, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products.

On the basis of the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Regarding the appropriate and suitable test method, the method will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the simulation study also requested in this decision, or by some other measure. You will need to provide a scientifically valid justification for the chosen method.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section

R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

16. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a report of the concentration test results for tris(2-ethylhexyl)benzenetricarboxylate(said to follow OECD TG 305 C) with the analogue substance TOTM (1,2,4-benzenetricarboxylic acid, tris(2-ethylhexyl) ester; EC number 222-020-0), which was reported as weight of evidence.

You also have sought to adapt this information requirement according to Annex XI, Section 1.3. of the REACH Regulation by providing a QSAR model applied to the main constituent of your substance, namely [redacted].

However, as explained above in Appendix 1, sections 0.1. and 0.2 of this decision, your adaptations of the information requirement cannot be accepted.

Based on the information provided on this endpoint for the registered substance in the technical dossier, the information requirement is not met. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have provided comments on this decision and the absence of conditional request as per the PBT approach so that P has to be shown first to then continue for B testing.

ECHA has accounted for your comments and with regard to the other decision for TM8 would like to repeat that under DEv (dossier evaluation decision processing) you may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. In line with the PBT assessment guidance, ECHA would like to remind that in deciding which information is required on persistence, bioaccumulation or toxicity in order to arrive at an unequivocal conclusion, care must be taken to avoid vertebrate animal testing when possible. This implies that, when for several properties further information is needed, the assessment should normally focus on clarifying the potential for persistence first. When it is clear that the P criterion is fulfilled, a stepwise approach should be followed to elucidate whether the B criterion is fulfilled, eventually followed by toxicity testing to clarify the T criterion.

ECHA agrees that the need for further information on bioaccumulation related to outcome of the simulation tests is also requested in this decision. ECHA notes that you shall provide information on the registered substance, including all relevant constituents, impurities and additives present in concentration of ≥ 0.1% (w/w). Alternatively, you shall provide a justification for why you consider certain constituents, impurities or additives present in concentration of ≥ 0.1% (w/w) or certain constituent fractions/blocks as not relevant for the PBT/vPvB assessment.

ECHA acknowledges your commitment to perform experimental measurements of log K_{ow} on the registered substance or its constituents.
The log K_{ow} estimation provided by you in the technical dossier, is referring to one constituent

only of the UVCBs. Thus, it does not represent the behaviour for the all constituents nor does it show definitively how the constituents, impurities or its degradation products will behave in the environment or their bioaccumulative properties. ECHA notes that not only one value for K_{ow}, but the range of values or corresponding measurements obtained for the different constituents is needed, in order to further provide with screening information.

Consequently, the request for OECD TG 305 is maintained as an information requirement.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* (version 3.0, June 2017) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2. The ECHA Guidance defines further that results obtained from a test with aqueous exposure can be used directly for comparison with the B and vB criteria of Annex XIII of REACH Regulation and can be used for hazard classification and risk assessment. Comparing the results of a dietary study with the REACH Annex XIII, the B and vB criteria are more complex and have higher uncertainty. Therefore, the aqueous route of exposure is the preferred route and shall be used whenever technically feasible.

If you decided to conduct the study using the dietary exposure route, you shall provide scientifically valid justification for your decision. Data obtained from a dietary study will also need to be used to estimate BCF values.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit, the following information derived with the registered substance subject to the present decision: Bioaccumulation in fish: aqueous or dietary bioaccumulation fish test (test method: OECD TG 305).
You shall provide information on the degradation of all relevant constituents, impurities and additives present in concentration of ≥ 0.1% (w/w). Alternatively, you shall provide a justification for why you consider certain constituents, impurities or additives present in concentration of ≥ 0.1% (w/w) or certain constituent fractions/blocks as not relevant for the PBT/vPvB assessment.

Notes for your consideration

Before conducting the above test you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), Chapter R.11.4. and Figure R.11-4 on the PBT assessment for further information on the integrated testing strategy for the bioaccumulation assessment of the registered substance. You should revise the PBT assessment when information on bioaccumulation is available.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 30 November 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

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

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-55 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2019.

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

3. 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 your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.