EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For ditolyl ether (DTE), CAS No 28299-41-4 (EC No 248-948-6)

Addressees: Registrant(s)[1] of ditolyl ether

This decision is addressed to the Registrant(s) of the above substance with active registrations pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by Bureau REACH on behalf of the Ministry of Infrastructure and the Environment as the Competent Authority of the Netherlands (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 31 August 2014, i.e. the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of the Netherlands has initiated substance evaluation for the registered substance ditolyl ether (DTE), CAS No 28299-41-4 (EC No 248-948-6) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to environment (suspected PBT/vPvB) and to exposure (high aggregated tonnage), the registered substance was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of the Netherlands was appointed to carry out the evaluation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of Registrant(s) addressed by the decision.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding environmental risks.

The evaluating MSCA (eMSCA) did not assess any endpoint regarding potential concerns of the registered substance on Human Health. The evaluating MSCA considered that further information was required to clarify the abovementioned environmental and exposure concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 26 March 2015.

On 4 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant(s) commenting phase

By 10 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s).

On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 3 March 2016 the eMSCA notified the Competent Authorities of the other Member States and ECHA of the draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 8 April 2016 ECHA notified the Registrant(s) of the proposals for amendments to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

Referral to Member State Committee

On 18 April 2016 ECHA referred the draft decision to the Member State Committee.

By 10 May 2016 in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposal(s) for amendment. In addition, the Registrant(s) provided comments on the draft decision. The MSC took the comments on the proposal(s) for amendment of the Registrant(s) into account. The MSC did not take into account the Registrant(s)' comments on the draft decision as they were not related to the proposal(s) for amendment made and are therefore considered outside the scope of Article 52(2) and Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 23 May 2016 in a written procedure launched on 13 May 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods and instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance ditolyl ether (DTE) subject to the present decision:

1. **Identification of the [redacted]% w/w impurity of the registered substance, down to 0.1% w/w;**

2. **Vapour Pressure (test method: OECD TG 104, 2006 or EU method A.4);**

3. **Information on the Exposure Scenarios of the Chemical Safety Report (CSR):**
   a. Information on operational conditions, prevention measures, risk management options, releases and emissions for each specific exposure scenario (manufacturing and all registered industrial uses);
   b. An update of all Exposure Scenarios, including the release factors for use at industrial site, i.e. industrial use as heat transfer fluid; industrial use as intermediate; industrial use as monomer for the production of leather and textile processing agents; industrial use as processing aid; and industrial use as laboratory chemical;
   c. Information on the calculations of Predicted Environmental Concentrations (PECs) for manufacture, formulation, industrial use, professional use and the waste stage in section 9 of the CSR.

4. **Aerobic Mineralisation in Surface Water - Simulation biodegradation test (test method: OECD TG 309, 2004, EU method C.25) with the registered substance.** The test should be performed at an environmentally realistic ambient temperature of 12 degrees Celsius with a test set-up enabling to check the mass balance, using radiolabelled DTE, and the identification of transformation products relevant for Peristency, Bioaccumulation and Toxicity (PBT) assessment (at a concentration of ≥ 0.1 % w/w). The test shall include the determination of separate biodegradation rates for each individual isomer of the registered substance, i.e. 2,2′-; 2,3′-; 2,4′-; 3,3′-; 3,4′ and 4,4′-ditolylether;

If the registered substance, i.e. one or more of the DTE isomers, is considered persistent (P) or very persistent (vP) according to the Annex XIII criteria, the following information shall be provided:

5. **Bioaccumulation in Fish, aqueous exposure (test method: OECD TG 305, 2012, EU method C.13) with the registered substance.** The test should be performed with a test set-up enabling to check the mass balance, using radiolabelled DTE, and the identification of major transformation products. Excessive fish growth and lipid increases should be avoided, since these might confound the results. The results should be corrected for growth and normalized to 5% lipid content. The test shall include the determination of Bioconcentration Factor (BCF) values for each individual isomer of the registered substance, i.e. 2,2′-; 2,3′-; 2,4′-; 3,3′-; 3,4′ and 4,4′-ditolylether;

If one of the DTE isomers meets the criteria for vPvB in accordance with REACH Annex XIII, requests 6, 7, and 8 hereafter do not need to be adressed. However, if the outcome of the bioaccumulation test shows that the registered substance, i.e. one or more of the DTE isomers should be considered bioaccumulative (B) or very bioaccumulative (vB), in addition to being persistent (P) or very persistent (vP), the following information shall be provided for the isomer with the highest BCF value:

6. **Freshwater Algae and Cyanobacteria, Growth Inhibition Test (test method: OECD TG 201, 2006, EU method C.3) with the algae species *Desmodesmus subspicatus* for the individual isomer of DTE that has the highest BCF as determined in request (5) above.** ;
   - In addition to the test method, additional sampling for exposure concentrations should be done at minimum nine times between and including t = 0 and 72 hours at regular time intervals throughout the experiment.
   - Exposure concentrations shall be recalculated based on a time-weighted average;

In case the T criteria are not fulfilled based on the outcome of the toxicity test with algae and all other relevant available data, the following information shall be provided for the isomer with the highest BCF value:

7. ***Daphnia magna* Reproduction Test (test method: OECD TG 211, 2012, EU method C.20) for the individual isomer of DTE that has the highest BCF as determined in request (5) above.**
   - In addition to the test method, sampling for exposure concentrations shall be done at minimum six times between t = 0 and 21 days, evenly spread for semi static tests. For flow-through systems, sampling shall be done at minimum eight times between t = 0 and 21 days, with three sampling points in the first week to ensure stable test conditions. Samples for analysis shall be systematically changed amongst replicates.
   - Exposure concentrations shall be recalculated based on a time-weighted average, as described in OECD TG 211, Annex 6;

In case the T criteria are not fulfilled based on the outcome of the toxicity test with algae, daphnids and all other relevant available data, the following information shall be provided for the isomer with the highest BCF value:

8. **Fish, Early-life Stage Toxicity Test (test method: OECD TG 210, 2013) for the individual isomer of DTE that has the highest BCF as determined in request (5) above.**
   The test shall be conducted in a flow-through system, following species specific recommendations;
   - In addition to the test method, prior to initiation of the exposure period, proper function of the chemical delivery system across all replicates shall be ensured by measuring the test concentrations.
   - Throughout the experiment, sampling for exposure concentrations shall be done three times a week at regular time intervals, changing systematically amongst replicates.
   - Exposure concentrations shall be recalculated based on a time-weighted average;

Furthermore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit full study reports for the information required under points 1 to 8 of this Section II. The same analytical method should be used for the simulation biodegradation, bioaccumulation and the toxicity studies requested (requests 4, 5, 6, 7 and 8).

Based on the current information in the registration dossiers, the information as specified above is required. Nevertheless the evaluation of the information submitted in response to these requests might reveal that the safety of the registered substance still cannot be adequately assessed and might lead to additional requests for information.

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA an update of the registration dossier(s) containing either the information requests 1, 2, 3, 4 and 5 by **22 July 2019** or the information requests of 1, 2, 3, 4, 5, 6, 7 and 8 by **20 October 2021**[2], as well as an updated PBT assessment, including robust study summaries and, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing or other sequential information gathering or information generation approaches as appropriate.

III. Statement of reason

1. Identification of the [redacted]% w/w impurity of the registered substance, down to 0.1% w/w.

Establishing the concern
The Registrant(s) have listed the composition of the registered substance in the CSR (chapter 1.2, table 2 & 3), including the main constituents and the impurities. The lowest impurity listed is [redacted]% w/w [redacted]. However, there is one remaining impurity of [redacted]% that is not identified.

Justification why new information is needed
The unidentified impurity could be one or more chemical(s) with similar characteristics to the main constituents or the impurities already listed, which might be potential PBT substances. The entire composition of the registered substance should be clarified at least down to impurities of 0.1% w/w, as it has to be excluded that the substance contains PBT, vPvB or Substances of Very High Concern (SVHC) constituents.

What is the request
ECHA requests molecular identification of the remaining [redacted]% w/w unknown impurities of DTE.

Consideration of Registrants' comments
As a response to the request, the Registrant(s) noted that according to the currently available GC-MS analysis (GC-MS-study report as contained in section 1.4 of REACH registration dossier) there are three peaks above 0.1% (0.43%, 0.15% and 0.16%) in addition to the DTE isomer peaks. Their mass chromatogram exhibits signals for m/z = 198 and they are assumed to be isomeric to DTE by the Registrant(s). These three impurities >0.1% elute shortly (with retention times of 12.8-13.4 min) after the DTE isomers (with retention times of 11.5-12.7 min). ECHA is of the opinion that the information provided by

[2] The deadline set by the decision already takes into account the time that Registrant(s) may require to agree on who is to perform any required tests and the time that ECHA would require to designate a Registrant(s) to carry out the test(s) in the absence of the aforementioned agreement by the Registrant(s) (Article 53(1) of the REACH Regulation).

the Registrant(s) may be sufficient to characterise the impurities, however it is insufficient for a scientifically justified identification of the impurities.

The Registrant(s) further noted that these three impurities must be considered to be somewhat more polar based on the slightly higher retention times in GC. This interpretation is not agreed upon by ECHA, since higher retention times in GC are an indication of less polar characteristics of molecules.

Additionally, the Registrant(s) noted that according to the same GC-MS analysis, other unknown impurities are clearly below 0.1%. This could not be verified, as it was not clear to ECHA how exactly all impurity peaks, shown in the GC-MS chromatogram, were quantified. The Registrant(s) did not provide supporting information on standards nor a calibration curve.

Furthermore, ECHA also observed a fourth peak in the RI10/1000 track of the GC-MS ion chromatogram that was not specified by the Registrant(s).

Taken into account this information, ECHA is of the opinion that the unknown impurities are not sufficiently clarified and identified. Because of this,the request was not amended.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following information for the registered substance subject to this decision:
Identification of the [redacted]% w/w impurity of the registered substance, down to 0.1% w/w.

2. Vapour Pressure (test method : OECD TG 104, 2006 or EU method A.4).

Establishing the concern
The current vapour pressure (0.12 $Pa.m^3/mol$ at 20 °C) reported in the CSR is extrapolated from 130 degrees Celsius (based on a dynamic method) to 20 degrees Celsius. For compounds with a vapour pressure of 0.12 $Pa.m^3/mol$, suitable test guidelines exist for the determination of the vapour pressure of DTE without the need for extrapolation (Vapour Pressure, OECD TG 104, 2006).
The vapour pressure is a very important physical-chemical property that determines the way PBT testing is carried out, as well as exposure assessments.

Justification why new information is needed
If the vapour pressure is not accurately determined, the volatility might be over- or underestimated, which in turn influences the PBT assessment, as well as the exposure assessment.

What is the request
The request is to perform the following test: Vapour Pressure (test method: OECD TG 104, 2006 or EU method A4).

Consideration of Registrants' comments
The Registrant(s) agreed to perform a new study on the vapour pressure according to OECD 104 and to update the CSR with this new data.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision:
Vapour Pressure (test method: OECD TG 104, 2006 or EU method A4).

3. Information on the Exposure Scenarios of the Chemical Safety Report

Justification why new information is needed
Section 9 of the CSR listed the exposure scenarios that are employed in the chemical safety assessment. For all registered uses, the Registrant(s) stated that the substance is only used under strictly controlled conditions and no emissions to the environment occur. There was no evidence provided to justify the deviations from the default release factors to estimate emissions to the environment.
Also, this assumption is not in line with chapter 2 of the CSR, where it is indicated that 0% of the substance is registered as "uses as intermediate under strictly controlled conditions". The concern is that the actual release of the substance into the environment is larger than 0% and that the predicted environmental concentrations (PECs) are higher than currently reported.

What is the request
Pursuant to Article 46(1) of the REACH regulation the Registrant(s) shall submit the following information regarding the registered substance subject to the present decision:

a) Information on operational conditions, prevention measures, risk management options, releases and emissions for each specific exposure scenario (manufacturing and all registered industrial uses).

   The Registrant(s) indicated in the CSR that either water is collected for treatment at an Sewage Treatment Plant (STP) (manufacturing scenario) or no water is released (use scenarios, closed system or strictly controlled system). However, details to prove the validity of these arguments are lacking, meaning that no information is provided on how waste waters are collected, how facilities are cleaned, how cleaning water is subsequently discharged, and what operational conditions for strictly controlled systems are used. Overall, each specific exposure scenario should be self-explanatory with scientifically justified information for each environmental compartment.

b) An update of all Exposure Scenarios, including the release factors for use at industrial sites, i.e. industrial use as heat transfer fluid; industrial use as intermediate; industrial use as monomer for the production of leather and textile processing agents; industrial use as processing aid; and industrial use as laboratory chemical.

   The Registrant(s) currently indicated in the CSR that no emission to the environment takes place for the various industrial use exposure scenarios. However, the substance is not registered as "intermediate used under strictly controlled conditions" and thus not "exempted from the CSR". Therefore, default emissions are to be expected and the default release factors should be used in the exposure scenarios. Otherwise, clear evidence why deviation from the default factors is justified should be provided. Such evidence would be monitoring data or location and process specific required operational conditions and risk management options.

c) Information on the calculations of PECs for manufacture, formulation, industrial use, professional use and the waste stage in section 9 of the CSR.

   It was not possible to follow the approach used to calculate the PEC by the Registrant(s). For instance, the influent and effluent concentration of the local STP was measured and reported in the CSR (Table 47. Local releases to the environment, CSR) for the manufacturing scenario. However, the Registrant(s) used the effluent

data to calculate an influent concentration, which in turn was used to refine the risk assessment. It was not clear why the calculated influent concentration was used instead of the measured value.
Furthermore, it is requested that the Registrant(s) indicate the software and version number used for the PEC values at local and regional scale in the CSR (e.g. EUSES, ECETOC TRA, etc.), whenever relevant.

Consideration of Registrants' comments
The Registrant(s) responded by stating that the exposure scenarios will be revised in the dossier, and that the comments provided by the eMSCA will be taken into account.

With regard to emission to soil during manufacturing, the Registrant(s) justified the emission estimate to soil of 0% based on the argumentation that facility floors are impervious, rising water is collected and STP sludge is incinerated (not applied on land). This argumentation is very general and lacks detailed justification. ECHA requests that if emission estimates of 0% are used, this is justified with monitoring data or location and process specific required operational conditions and risk management options. The request is updated accordingly.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following information on the registered substance subject to this decision:

a) Information on operational conditions, prevention measures, risk management options, releases and emissions for each specific exposure scenario (manufacturing and all registered industrial uses).
b) An update of all Exposure Scenarios, including the release factors for use at industrial sites, i.e. industrial use as heat transfer fluid; industrial use as intermediate; industrial use as monomer for the production of leather and textile processing agents; industrial use as processing aid; and industrial use as laboratory chemical.
c) Information on the calculations of PECs for manufacture, formulation, industrial use, professional use and the waste stage in section 9 of the CSR.

4. Aerobic Mineralisation in Surface Water - Simulation biodegradation test (test method: OECD TG 309, 2004) with the registered substance.

Establishing the concern
The registered substance is not ready biodegradable and not inherently biodegradable, with degradation amounting to 2% and 3% respectively. Since the registered substance is not sufficiently mineralised within 28 days (≥ 60%), the concern is that the registered substance is persistent. Furthermore, as the registered substance consists of several isomers, with different ortho-, meta- and para-substitution, there is additional concern that these isomers might differ in environmental fate and effect. As there are currently only screening studies available that assessed the isomeric mix, a simulation study is needed to confirm whether the individual isomers of the registered substance meet the P or even the vP criterion.

Justification why new information is needed
A simulation test will provide insight in potential long term degradation of the individual isomers of the registered substance and their potential degradation products under more environmentally relevant conditions. There is a PBT concern for the parent compound and potential breakdown products. Therefore, a simulation study is needed to assess the persistency of the individual isomers of the registered substance and to identify formed degradation products.

What is the request
The Registrant states in the CSR that the predominant emission of the registered substance to the environment will be through waste water from manufacturing, transferred to sewage treatment plants (STPs) (CSR 4.1.2.1.2.). EPISUITE's (2012) fugacity model shows that 95% of the ditolyl ether emitted in the environment will end up in soil and 3.4% in water with the estimated reported release pattern and total release of the substance per year (CSR 10.2). The release pattern is however somewhat uncertain. For comparison, almost 11 % of the relative mass of the registered substance ends up in surface water with the default emission pattern with equal emission to air, water and soil according to the freely available "Unit World" fugacity Environmental partitioning model included in the EPIWIN software package v. 4.1 (freely downloadable from: http://www.epa.gov/oppt/exposure/pubs/episuite.htm) and according to EPIWIN's STP model around 50 % will pass through to surface water indicating that surface water may be significantly exposed if the registered substance is released to the sewage system.

Although the fugacity model shows that a significant fraction of the emitted DTE may end up in the soil, also surface water seems to be a compartment of concern and therefore ECHA requests the Water Simulation biodegradation test, rather than the Soil Simulation test. The interpretation of the Water Simulation test is straightforward compared to the more complex soil simulation test that requires additional elaborate analytical procedures to determine an accurate mass balance over the (pore)water, soil and dissolved organic matter fractions for the registered substance. Supplementary sorption material needs to be used to measure possible losses by evaporation (as described in the guideline OECD TG 307) and a set up with four soils has to be used in order to obtain a biodegradation rate, as the primary goal of the guideline is identification of the transformation pathways and not their kinetics. For these reasons, it is considered more proportionate to request a Water Simulation Test. The Water Simulation test is suitable for lower, environmentally relevant, test concentrations and surface water is considered to be an equally relevant compartment for the registered substance as soil, due to the direct emission of STP effluents to surface water.

Suitable controls and precautions shall be required to prevent evaporation from the test vessels (closed flasks) as the Henry's law constant is larger than 1 Pa m^3/mol. Transformation products formed at levels of 1% w/w or more of the amount of test substance added shall be identified, with reasonable attempts made to quantify these down to 0.1% w/w. The test should be performed at the environmentally relevant temperature of 12 degrees Celsius. Also, a full mass balance shall be determined based on analytical measurements and using radiolabelled DTE. The test shall include the determination of separate biodegradation rates for each individual isomer of DTE, i.e. 2,2'-; 2,3'-; 2,4'-; 3,3'-; 3,4' and 4,4'-ditolylether.

Consideration of Registrants' comments
The Registrant(s) assumed that since the registered substance does not degrade in the screening tests, it will fulfil the criterion as P/vP. The Registrant(s) therefore proposed to focus on the B/vB criterion, and perform the simulation study only in case the registered substance is determined to be B/vB. The Registrant(s) also proposed to delay T testing until P/vP and B/vB is proven. The latter proposal, i.e. T testing only when proven that the registered substance meets the P and B criteria, is in accordance with the ECHA Guidance, and is agreed upon by ECHA. The guidance, however, prescribes that if a compound is not ready biodegradable and shows a lack of degradation in an inherent biodegradability test, it should be considered potentially persistent and a simulation biodegradation study is needed to confirm if it meets the P or vP criteria (ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11, version 2.0, November 2014). Considering that for the registered substance only screening tests are available, and that these tests show

that the registered substance is neither ready, nor inherently biodegradable, a biodegradation simulation study is needed to conclude on the definitive persistence status. Therefore, ECHA did not agree to deviate from the standard approach. In case the registered substance and its degradation turn out not to meet the P criteria, B testing is superfluous. Therefore, unnecessary animal testing might be prevented by first performing the Water Simulation test (request 4).

The Registrant(s) made three remarks with regard to the specified test conditions of the simulation test:

- Testing temperature: The Registrant(s) suggested that the timeline for the update of the registration is extended by 6 months, since 12°C is not the standard testing temperature. The Registrant(s) indicated that it might be difficult and time consuming to find a laboratory which ensures the demanded testing conditions.
  ECHA is of the opinion that the default test periods of 18 months for the simulation biodegradation test is sufficient to carry out the required study under the indicated test conditions. Also, as is common practice for the substance evaluation process, an additional 3 months are granted to allow the Registrant(s) to decide who will perform the test (already included in the currently provided deadlines). Although 12°C is currently not the standard test temperature, standard laboratory facilities or set-ups are regularly equipped to adjust climate conditions to the testing temperature required. Therefore, ECHA is of the opinion that the default 18 months, plus additional 3 months to agree who performs the test, are sufficient to find a qualified laboratory and perform the test using the requested testing conditions.

- Quantification method: The Registrant(s) indicated that they would welcome the authority to leave the decision on radiolabelling or not to the Registrant(s), who could then decide on the method to quantify the DTE isomers.
  ECHA is of the opinion that radiolabeling of the DTE isomers is required to obtain a scientifically reliable mass balance of the registered substance and its potential break-down products, throughout the simulation test. The OECD TG 309 (2004) also recommends using labelling for more reliable results. Therefore, the request for radiolabeling of the registered substance is not amended.

- Radiolabelled synthesis: the Registrant(s) assumed that the conditions of technical synthesis are not suitable for radioactive synthesis on small scale because of very harsh reaction conditions, which appear prohibitive for radioactive material. The Registrant(s) described an alternative route where each of the six isomers have to be synthesized in at least 9 individual reaction steps. Therefore, the Registrant(s) requested that the timeline for the update of the registration is extended by 4 months.

  This concern is acknowledged. However, the performance of the OECD TG 309 will take a maximum of 6 months, which includes a maximum of 90 days of the actual test duration with an additional incubation time of 3 months. Since the total timeline of the OECD TG 309 is 18 months, ECHA is of the opinion that there is sufficient time to synthesize the radiolabeled substances. As a consequence, the request was not amended.

Considerations of proposals for amendment and Registrant(s)' comments on them
One proposal for amendment (PfA) suggested to add more details of the fugacity models to show that water may be a compartment of concern. This information was added.

Another PfA suggested to delete the requirement to measure the degradation half-life of individual impurities. The request for testing impurities >0.1% was removed in order to

follow a less burdensome testing strategy. The current decision will focus on the six isomers of DTE (2,2'-; 2,3'-; 2,4'-; 3,3'-; 3,4'- and/or 4,4'-ditolylether). The dimethylnaphthalene (isomers) do not exceed the B screening criterion of log Kow >4.5, and thus it is not deemed necessary to assess their persistence. The need for testing of the unknown impurities will be evaluated after the identification as requested in the current decision (request 1).

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Aerobic Mineralisation in Surface Water – Simulation Biodegradation test (test method: OECD TG 309, 2004) with the registered substance.

5. Bioaccumulation in Fish, aqueous exposure (test method: OECD TG 305, 2012) with the registered substance.

This testing is only required if the registered substance, i.e. one or more of the DTE isomers, is considered persistent (P) or very persistent (vP) according to the Annex XIII criteria.

Establishing the concern
The bioaccumulative properties of the registered substance were estimated based on read-across studies of the non-substituted diphenyl ether. When the read-across is performed according to the guidance (ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014), there are indications that the bioconcentration factor (BCF) of the registered substance exceeds the trigger value of 2000.

Justification why new information is needed
The Registrant(s) derived a BCF for the registered substance of 982, based on a read-across with diphenyl ether with an experimental BCF of 196 for fish.

According to the ECHA Guidance (Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014), for each methyl group the log K_{OW} will be 0.5 higher and the estimated BCF should be multiplied by a factor of 10^0.5. Since the registered substance has two methyl groups more than diphenyl ether, this means that the BCF of the registered substance will result in an increase of log K_{OW} value with a factor of 10^1 hencethe estimated BCF should be multiplied by a factor of 10, resulting in a BCF of 1960 for the registered substance.
The Registrant(s) was of the opinion that correcting twice with a factor of 10^0.5 for both methyl groups is too conservative. Instead, he used a factor of 10^0.7, thereby deriving a BCF of 982. However, a justification for using this factor was not given in the CSR. Therefore, ECHA is of the opinion that there is no reason to deviate from the guidance. The ECHA Guidance further prescribes that if a BCF based on the use of read-across is close to the threshold of 2000, the use of read-across is inadequate and experimental verification is necessary.

Furthermore, the Registrant(s) used a BCF of 196 for diphenyl ether, where additional BCF studies performed with diphenyl ether with a reliability score of 2 are available (CSR). These studies indicated BCF's for diphenyl ether ranging from 50 to 594. Guidance prescribes that generally the highest valid reported BCF should be used for the PBT assessment if multiple reliable values are present (ECHA, CSA R.7c endpoint specific guidance, 2014). Applying a correction factor of 10^1 to the value of 594, will yield a BCF of 5940. Since this is above the trigger value of 2000, experimental verification is requested

to address this concern.

Isomer specific bioaccumulation
The registered substance consists of several isomers, with different ortho-, meta- and para-substitution. Different isomers can have different log K_{OW} values and therefore different bioaccumulation potential. This is illustrated by predictions derived by the EPISUITE BCFBAF model, based on the log K_{OW} value of 5.15 for the 3,3'- and 3,4'-DTE isomers and based on the log K_{OW} of 4.30 for the 2,3'- and 2,4'-DTE isomers. The isomers with predicted higher log K_{OW} have an estimated BCF of 2578 (upper trophic, Arnot Gobas method) and 1151 L/kg wet-wt (regression based method). The isomers with the predicted lower log K_{OW} have an estimated BCF of 321.3 and 994.5 L/kg, respectively. As DTE is estimated to be borderline B by the read-across, some of the individual isomers might already fulfil the B criterion. In the bioaccumulation read-across all isomers were assessed together and this might conceal isomer specific behaviour, hampering an individual assessment of each of the main constituents of DTE. Insight in the individual BCF values of each isomer will clarify whether the isomers might have different bioaccumulation properties. Experimental verification is necessary in order to assess the bioaccumulation of the registered substance.

What is the request
ECHA requests a bioaccumulation study in fish, from which an individual BCF value for each isomer of the registered substance can be estimated. A full mass balance should be determined based on analytical measurements and using radiolabelled DTE. During this test the organic carbon content of the test water should be kept as low as possible, and efforts shall be made to establish the truly dissolved concentration, for example by taking measurements of particulate and dissolved organic carbon concentrations at appropriate time points and using an appropriate technique to enable the estimation of the bioavailable fraction if feasible (e.g. solid-phase microextraction). Excessive fish growth and lipid increases shall also be avoided, since these might confound the results. The results shall in any case be corrected for growth and normalized to 5% lipid content.

The registered substance has moderate water solubility (2.8 mg/L) and is hydrophobic (log K_{OW} = 4.3-5.14 QSAR). It is also slightly volatile (P_v = 0.12 Pa.m^3/mol & H = 4.864 Pa m^3/mol). It could be considered a difficult substance for bioaccumulation testing as it fulfils the indicator values of S_W <100 mg/L, log K_{OW} >4 and H >0.1 Pa.m^3/mol, therefore guidance shall be consulted to help maintain or achieve the required exposure concentration (OECD TA 23[3]).

Consideration of Registrants' comments
The Registrant(s) noted that the eMSCA quoted outdated ECHA Guidance (2012), whereas a new version is available (v2.0, 2014). The eMSCA acknowledged this. The specific content to which the eMSCA referred to is identical in both the 2012 version and the updated guidance, only the page numbers shifted. The year and page numbers in the required references have been corrected.

Considering the endpoint bioaccumulation, the Registrant(s) requested to use calculated BCF data for the registered substance and avoid testing. However, the guidance prescribes that if BCF estimates are close to the trigger value, read across is inadequate (Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014) and experimental verification is necessary.

The BCF of DTE was calculated by the Registrant(s) as 982 L/kg based on a BCF of diphenyl

[3] OECD Series on Testing and Assessment Number 23, Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO(2000)6

ether of 196 L/kg multiplied by a factor of 10^0.7. The Registrant(s) explained that a factor of 0.7 was used to correct for the effect of the two additional methyl groups, because it is the difference between the log K_{OW} of 4.21, reported for diphenyl ether, and the log K_{OW} of 4.9, which was determined for ditolyl ether using the HPLC method. However, ECHA believes that the reported log k_{OW} value of 4.9 for DTE is not accurate, nor transparently validated. The log K_{OW} of the registered substance was determined as 4.9, using OECD TG 117 (HPLC-method). This method is precise by having a low standard deviation, but it is less accurate than the slow-stirring method (OECD TG 123). The registered substance consists of several isomers, with different ortho-, meta- and para-substitution. The Registrant(s) showed that the isomers may have dissimilar log K_{OW} values, which in turn may result in different environmental fate and effects. Thus, this log K_{ow} value might not be representative for all DTE isomers. Therefore, ECHA does not consider it scientifically justified to use this log K_{OW} value of DTE to estimate the BCF.

The correction factor of 0.5 per methyl group is, besides prescribed by the guidance (Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014) is supported by the following example; naphthalene has an experimental log K_{OW} value of 3.30 (Hansch C. et al, 1995[4]), while dimethyl naphthalene isomers have an experimental log Kow value from 4.26 to 4.44 (Table 3, Registrant(s)' Endpoint specific comments to the draft decision, Endpoint 3). This demonstrates that a correction factor of 0.5 per methyl group may be needed and indeed two methyl groups increase the log K_{OW} value with a factor of 10^1.

Additionally, it is pointed out that supporting read-across studies (reliability 2), also reported by the Registrant(s), have BCF values ranging from 50 to 594. Guidance prescribes that generally the highest valid reported BCF should be used for the PBT assessment (e.g. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014, page 49) if multiple reliable values are present. Applying a correction factor (either the 10^0.7 proposed by the Registrant or the 10^1 of the guidance) will yield an estimated worst case BCF of 2977 or 5940, far above the trigger value of 2000. The request was amended to include this specification.

ECHA concluded that the BCF estimates, based on either the log K_{OW} value or on the read-across from diphenyl ether, both did not sufficiently take away the B concern and did not prove that DTE will not meet the B criterion. Therefore, experimental verification is required in order to exclude bioaccumulation of the DTE isomers and ECHA did not adapt the request considering this endpoint.

Bioaccumulative properties of the impurities of DTE
The Registrant(s) stated that a bioaccumulation study is not considered necessary for assessing the impurities ≥0.1%. With regard to the isomeric dimethylnaphthalene impurities, it was agreed that the screening criterion for B/vB of log K_{OW} ≥4.5 is not fulfilled and that therefore a bioaccumulation study is not needed. The request was adopted accordingly.

The remaining unknown impurities >0.1% w/w have not yet been identified. As they might be more lipophilic than the DTE isomers, it cannot be excluded that they fulfill the screening criterion. However, the eMSCA will first evaluate the results that will become available based on this decision, including the identity of these impurities, before deciding on the need for performing a bioaccumulation study for these impurities.

[4] Hansch. C., A. Leo and D. Hoekman. 1995. Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Professional Reference Book. Washington, DC: American Chemical Society.

Considerations of proposals for amendment and Registrant(s)' comments on them
One PfA suggested to delete the requirement to measure the BCF values of individual impurities. ECHA would like to note that all constituents >0.1% w/w could be relevant for the PBT assessment. However, the request for testing impurities >0.1% was removed in order to follow a less burdensome testing strategy, since in case the isomers are confirmed as PBT/vPvB there is no need for additional information on the impurities. The current decision will focus on the six isomers of DTE (2,2'-; 2,3'-; 2,4'-; 3,3'-; 3,4'- and/or 4,4'-ditolylether). The dimethylnaphthalene (isomers) do not exceed the B screening criterion of log Kow >4.5, and thus it is not deemed necessary to derive their BCF. The need for testing of the unknown impurities will be evaluated after the identification as requested in the current decision.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Bioaccumulation in Fish, aqueous exposure (test method: OECD TG 305, 2012) with the registered substance. The test shall include the determination of separate BCF values for each individual isomer of the registered substance, i.e. 2,2'-; 2,3'-; 2,4'-; 3,3'-; 3,4' and 4,4'-ditolylether. This testing is only required if the registered substance, i.e. one or more of the DTE isomers, is considered persistent (P) or very persistent (vP) according to the Annex XIII criteria.

6. Freshwater Algae and Cyanobacteria, Growth Inhibition Test (test method: TG OECD 201, 2006) with the algae species *Desmodesmus subspicatus* for the individual isomer of DTE that has the highest BCF as determined in request (5) above.

Establishing the concern
The 72 hour NOEC of the registered substance for the algae *Desmodesmus subspicatus* is 0.01 mg/L (growth). This value is at the T criterion. The concern is that one or more of the different isomers of the registered substance will show toxicity values that are below 0.01 mg/L and will fulfil the T criterion.

Justification why new information is needed
In the toxicity tests summarized in the CSR, all isomers were tested together and this might conceal isomer specific toxicity, hampering an individual toxicity assessment of each of the main constituents of the registered substance. The individual isomers might be more toxic leading to a lower NOEC and fulfilling the T criterion.

What is the request
The request is to perform a Growth Inhibition test with the individual isomer of DTE that is considered (v)P and (v)B according to Annex XIII and that has the highest BCF value as determined in request (5) the bioaccumulation study. The test should be performed with the algae species *Desmodesmus subspicatus*. This request does not need to be adressed if one of the DTE isomers meets the criteria for vPvB in accordance with REACH Annex XIII.

The registered substance should be considered a difficult substance for aquatic toxicity testing, therefore guidance shall be consulted to help maintain or achieve the required exposure concentration (OECD TA 23[5]). Suitable controls and precautions will be required to prevent evaporation from the test vessels (closed flasks) as the Henry's law constant is larger than 1 Pa m^3/mol.

[5] OECD Series on Testing and Assessment Number 23, Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO(2000)6

As it is also a lipophilic substance, losses may also occur to growing algae and test vessels. Therefore, a fast decrease of exposure concentration is expected. This should be monitored by verifying the exposure concentration at regular time intervals by analytical measurements throughout the experiment. Sampling for exposure concentrations should be done at minimum nine times between and including t = 0 and 72 hours at regular time intervals throughout the experiment. These samples should be analysed directly upon sampling and not stored for later analysis. Exposure concentrations should be recalculated based on a time-weighted average.

Consideration of Registrants' comments
The Registrant(s) asked why the NOEC of 0.01 mg/L of the algae toxicity study is referred to instead of the EC_{10} of 0.02 mg/L. It is clarified that indeed the EC_{10} is above the criterion, where the NOEC is not. This means that based on these toxicity test results, the registered substance should be considered borderline T or not T. Since the registered substance consists of several isomers, ECHA is concerned that one or more isomers will fulfil the T criterion. Therefore, it is deemed necessary to determine whether the individual isomers of the registered substance will meet the T criterion.

The Registrant(s) proposed to perform a new algae inhibition test with two groups of DTE isomers, group 1 and 2. However, ECHA did not agree with this grouping approach for testing. The Registrant(s) indicated to prefer testing of the individual isomers over testing of additional algal species, as was requested initially. A request was added to perform a new algae inhibition test with the six main isomers of DTE and impurities >0.1% w/w, for those that meet the criteria for persistence (v)P and bioaccumulation (v)B according to Annex XIII.

The request was amended accordingly.

Finally, the Registrant(s) were "*deeply surprised and confused that the authority seems already to know that additional testing will result in lower NOEC fulfilling the T criterion*" and requested to adjust the statement in the request that isomers may fulfil the criterion, instead of plausibly will fulfil the criterion. It is noted that the process of substance evaluation is to do a PBT assessment, based on the concern that a compound or any of its constituents may be P, B and/ or T. It was not stated that DTE is toxic, merely that individual isomers might be T, as explained above. Since the word "*plausibly*" may be misinterpreted, this word was removed and the statement was adjusted correspondingly.

Considerations of proposals for amendment and Registrant(s)' comments on them
One MSCA suggested to specify in the request the algal species *Desmodemus subspicatus*, because that species was previously used in the algal growth inhibition study conducted with the registered substance, i.e. the isomeric mixture, and because that study showed that the registered substance was at or just above the T criterion. It is thus possible that for one or more of the different DTE isomers, toxicity values will be obtained that are below 0.01 mg/L when tested in *D. subspicatus.* The proposed specification of the algae species was accepted and the request amended accordingly.

Two PfAs suggested not to request toxicity testing in case the registered substance can be considered as meeting the vPvB criteria. It was agreed that a less burdensome testing strategy could be followed in order to avoid unnecessary use of resources. It was recognised that for any compound that meets the vPvB criteria, ecotoxicity testing will not be required and has amended the request accordingly to make this explicit.

One PfA furthermore suggested to perform the requested toxicity test on the isomer or impurity that leads to the greatest concern and is most likely to meet the T criterion. Based

on the current state of knowledge, no specific mode of action is expected for ditolyl ether (neutral organic, narcotic) and the most bioaccumulative isomer (highest BCF) is expected to be the most toxic to aquatic organisms. The revised testing strategy proposed was adopted. Concerning the testing of the other isomers and impurities >0.1% that meet the P/vP and B/vB criteria, there were proposals to remove the request from this current decision. It is noted that all constituents >0.1% could be relevant for the PBT assessment, but the request for testing impurities >0.1% was removed in order to derive a less burdensome testing strategy. Thus, ECHA restricted in the current decision the request for the algal toxicity test to the ditolyl ether isomer with the highest measured BCF that leads to the greatest concern and is most likely to meet the T criterion.

ECHA would like to stress that the testing strategy is kept as least burdensome as possible, as no further toxicity testing, i.e. request 7 and 8, is required if the DTE isomer that leads to the greatest concern will meet the T criterion based on the toxicity values obtained from the algal growth inhibition study.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Freshwater Algae and Cyanobacteria, Growth Inhibition Test (test method: OECD TG 201, 2006) with the algae species *Desmodesmus subspicatus* for the individual isomer of DTE that is considered (v)P and (v)B and that has the highest BCF as determined in request (5) above. If one of the DTE isomers meets the criteria for vPvB in accordance with REACH Annex XIII, the request does not need to be addressed.

7. *Daphnia magna* Reproduction Test (test method: OECD TG 211, 2012) for the individual isomer of DTE that is considered (v)P and (v)B and that has the highest BCF as determined in request (5) above.

If one of the DTE isomers is already found to meet the criteria for vPvB and/or PBT in accordance with REACH Annex XIII, this request does not need to be addressed.

Establishing the concern
The available chronic toxicity test on daphnids with the registered substance showed a NOEC = 0.057 mg/L (21 d, immobility). This value is close to the T criterion. The concern is that when individually tested, one or more of the different isomers of the registered substance will show toxicity values that are below 0.01 mg/L and will fulfil the T criterion.

Justification why new information is needed
In the toxicity tests summarized in the CSR, all isomers were tested together and this might conceal isomer specific toxicity, hampering an individual toxicity assessment of each of the main constituents of the registered substance. The individual isomers might be more toxic leading to a lower NOEC and fulfilling the T criterion. Therefore, it is preferred to determine the P, B and T criterion for each individual isomer, instead of the registered substance.

However, in order to follow the least burdensome testing strategy, the PBT assessment of this decision will be of the isomer that is currently of the highest concern, which is the isomer with the highest BCF value. Based on the current state of knowledge, no specific mode of action is expected for ditolyl ether (neutral organic, narcotic) and the most bioaccumulative isomer (highest BCF) is expected to be the most toxic to aquatic organisms.

What is the request
The request is to perform a *Daphnia magna* reproduction test with the individual isomer of

DTE that is considered (v)P and (v)B according to Annex XIII and that has the highest BCF value as determined in the bioaccumulation study (request 5). If one of the DTE isomers is already found to meet the criteria for vPvB and/or PBT in accordance with REACH Annex XIII, this request will not be required.

The registered substance should be considered a difficult substance for aquatic toxicity testing, therefore guidance shall be consulted to help maintain or achieve the required exposure concentration (OECD TA 23[6]). Suitable controls and precautions will be required to prevent evaporation from the test vessels (closed flasks) as the Henry's law constant is larger than 1 Pa m^3/mol.

As it is also a lipophilic substance, losses may also occur to organic matter and test vessels. Therefore, a fast decrease of exposure concentration is expected and exposure concentrations should be maintained as constant as possible using a semi-static or a flow-through system. This should be monitored by verifying the exposure concentration at regular time intervals by analytical measurements throughout the experiment, following the recommendations of OECD TG 211. Sampling for exposure concentrations shall be done at minimum six times between t = 0 and 21 days, evenly spread for semi static tests. For flow-through systems sampling shall be done at minimum eight times between t = 0 and 21 days, with three sampling points in the first week to ensure stable test conditions. Exposure concentrations should be recalculated based on a time-weighted average, as described in Annex 6 of OECD TG 211.

Considerations of proposals for amendment and Registrant(s)' comments on them

One PfA suggested to add a requirement to measure long-term *Daphnia* toxicity in accordance with the same strategy as the other aquatic toxicity tests (i.e. on a relevant constituent basis) as well as on the commercial substance. Such a test was deemed useful to check whether isomer-specific testing gives significantly different results compared to a test on the registered substance, i.e. the isomeric mixture. If there is no difference, testing on fish could be done using the commercial substance, which would minimise the number of vertebrates needed (based on the initial request where multiple DTE isomers might have been tested in fish). In addition, there may be no need to conduct fish testing at all if the results from the Daphnia toxicity testing showed that an isomer that is (v)P and (v)B, also meets the T criterion. The proposal was accepted and a requirement to measure long-term Daphnia toxicity was added.

Based on the PfAs received, the tiered aquatic toxicity testing strategy was adapted in order to become less burdensome and to avoid unnecessary use of resources. Firstly, no toxicity testing (request 6, 7 and 8) is required if a constituent of the registered substance can be considered as meeting the vPvB criteria. Secondly, instead of requesting toxicity tests on all ditolyl ether isomers and/or impurities >0.1% w/w that are considered (v)P and (v)B, the toxicity tests are requested for the ditolyl ether isomer with the highest measured BCF that leads to the greatest concern and that is most likely to meet the T criterion. Based on the current state of knowledge, no specific mode of action is expected for ditolyl ether (neutral organic, narcotic) and the most bioaccumulative isomer (highest BCF) is expected to be the most toxic to aquatic organisms. Following evaluation of the updated CSR, testing on the other isomers and impurities >0.1% that meet the P/vP and B/vB criteria, could be requested in a second substance evaluation decision. Thirdly, toxicity testing will stop as soon as the DTE isomer that leads to the greatest concern meets, in addition to the (v)P and (v)B criteria, the T criterion, with the ordering of testing being: algae, daphnia and

[6] OECD Series on Testing and Assessment Number 23, Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO(2000)6

finally fish. This tiered aquatic toxicity testing strategy minimizes the usage of test animals.

Consideration of Registrants' comments on the Proposals for Amendment (PfAs)
The Registrant(s) did not agree with the PfA to add a requirement to measure long-term *Daphnia* toxicity. The Registrant(s) stated that the dossier was updated recently to include a new *Daphnia* toxicity study and that the authority submitting the PfA may not have been aware of this. However, ECHA notes that in this specific *Daphnia* test, all isomers were tested together, as the registered substance, and this might conceal isomer specific toxicity (as addressed in the justification why this endpoint is needed). Therefore, it is preferred to determine the T criterion for each individual isomer, instead of the registered substance.

However, following the least burdensome testing strategy, the PBT assessment of this decision will be of the isomer that is currently of the highest concern, which is the isomer with the highest BCF value. Based on the current state of knowledge, no specific mode of action is expected for ditolyl ether (neutral organic, narcotic) and the most bioaccumulative isomer (highest BCF) is expected to be the most toxic to aquatic organisms. The *Daphnia* test should be performed before the long term fish study (endpoint 8), to minimize vertebrate testing. If the isomer with the highest BCF fulfils the T criterion based on the *Daphnia* test results, no further ecotoxicity testing is required.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: *Daphnia magna* Reproduction Test (test method: OECD TG 211, 2012) for the individual isomer of DTE that is considered (v)P and (v)B and that has the highest BCF as determined in request (5) above. If one of the DTE isomers is already found to meet the criteria for vPvB and/or PBT in accordance with REACH Annex XIII, this request does not need to be addressed.

8. Fish, Early-life Stage Toxicity Test (test method: OECD TG 210, 2013) for the individual isomer of DTE that has the highest BCF as determined in request (5) above.

If one of the DTE isomers is already found to meet the criteria for vPvB and/or PBT in accordance with REACH Annex XIII, this request does not need to be addressed.

Establishing the concern
The available acute toxicity test on fish with the registered substance reports an LC_{50} of 2.62 mg/L for *Danio rerio*. This value is nominal and the test was performed under static conditions. As the guidance states (Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c, version 2.0, November 2014), studies that involve only nominal exposure concentrations are unreliable unless adequate evidence is available from other studies to suggest that the test concentrations would have been well maintained. The registered substance is slightly volatile and under static conditions it is highly improbable that test concentrations were maintained throughout the duration of the experiment. The actual test concentrations might thus have been substantially lower than the nominal test concentrations in this acute toxicity test. Furthermore, there are no chronic toxicity data on fish available. The concern is that the registered substance may meet the T criterion based on chronic toxicity to fish.

Justification why new information is needed
Because it is highly improbable that the test concentrations were well maintained during the acute fish toxicity test, the results are unreliable and might underestimate the toxicity of the registered substance. Furthermore, there are no chronic toxicity data on fish available.

The effect concentrations, based on measured concentrations, shall be used for the PBT assessment, as well as for risk assessment purposes (e.g. PNEC derivation). Therefore, a new adequate chronic fish study is required where test concentrations of the registered substance should be kept as constant as possible, and where the actual test concentrations should be measured at regular intervals.

What is the request
The request is to perform a fish early-life stage toxicity (FELS) test with the individual isomer of DTE that is considered (v)P and (v)B according to Annex XIII and that has the highest BCF value as determined in the bioaccumulation study (request 5). Evaporation from the test vessels during the experiment shall be prevented and a flow through system shall be used.

During this test the organic carbon content of the test water should be kept as low as possible, and efforts shall be made to establish the truly dissolved concentration, as recommended by the OECD TG 210, for example by taking measurements of particulate and dissolved organic carbon concentrations at appropriate time points and using an appropriate technique to enable the estimation of the bioavailable fraction if feasible (e.g. solid-phase microextraction). Furthermore, in addition to the test method, prior to initiation of the exposure period, proper function of the chemical delivery system across all replicates should be ensured by measuring the test concentrations. In addition, the actual test concentrations shall be verified by analytical measurements, three times a week at regular time intervals throughout the experiment, changing systematically amongst replicates. Exposure concentrations shall be recalculated based on a time-weighted average.

Consideration of Registrants' comments
The Registrant(s) addressed the guidance to question whether the requested FELS test is appropriate, and stated the following: *"If a long-term test with daphnids or algae provides NOEC close to, but above 0.01 mg/L, a long-term fish study is said likely to be needed unless there is convincing evidence that the fish NOEC will be higher than 0.01 mg/L. Such supporting evidence is given to be that -an acute fish value that is a factor of 10 or more greater than that of the other two trophic levels under the provision that the acute daphnid test showed toxicity at least one order of magnitude lower than the limit of solubility-."*. The Registrant(s) elaborated this by noting that the LC50 of the available acute fish toxicity study is a factor 75, respectively, 16 higher than the acute effect concentrations reported for algae and daphnids, and that the ratio of toxicity to water solubility is 0.9. However, the Registrant(s) also acknowledged that the acute fish results were based on nominal concentrations. The Registrant(s) estimated, based on the recovery rates from the other available aquatic toxicity tests, an 85% loss of test item in the acute fish study. The Registrant(s) subsequently assumed a worst-case LC50 of 0.4 mg/L, which would roughly be a factor 11, respectively, 3 higher than the acute effect concentrations reported for algae and daphnids, as well as a factor 7 below water solubility.

The Registrant(s) concluded that the supporting evidence criteria outlined in ECHA Guidance (ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11, version 2.0, November 2014) were not met by the calculated factors, but were close to them when loss of test substance was accounted for in the acute fish toxicity test. It was recommended by the Registrant(s) to consider this in the decision to request an additional fish study in the final decision.

ECHA is of the opinion that the toxicity ratios, relation to water solubility or any other sensitivity factor cannot be derived or determined, because the present acute fish toxicity study reports effect concentrations that are based on nominal test concentrations.

The Registrant(s)' attempt to estimate the recovery of the registered substance for the available acute fish toxicity study is not considered appropriate. The recovery of a test compound is specific for different test set-ups and may vary from day to day even for the same set-up. This is why measured concentrations are important. Therefore, ECHA is of the opinion that these recovery estimates are not reliable and thus this cannot be used to estimate for the acute fish toxicity test a measured LC50 from the available nominal LC50.

The Registrant(s) proposed tiered toxicity testing, arguing that no additional testing with fish (vertebrates) should be requested for risk assessment purposes provided that the results from the requested algal growth inhibition test would fulfil the T criterion. This proposal is accepted. The Registrant(s) also noted that should the T criterion not be confirmed by additional testing on toxicity to algae and should the authority still request a FELS study for the PBT assessment and/or PNEC derivation in the final decision, then the study shall be performed as requested. This is considered acceptable by ECHA.

Considerations of proposals for amendment and Registrant(s)' comments on them
Two PfAs proposed that no toxicity testing is required in case the registered substance can be considered as meeting the vPvB criteria. It was agreed that a less burdensome testing strategy could be followed in order to avoid unnecessary use of resources. It was recognised that for any compound that meets the vPvB criteria, ecotoxicity testing will not be required and the request was adapted accordingly to make this explicit.

One PfA furthermore suggested to perform the requested toxicity test on the isomer or impurity that leads to the greatest concern and is most likely to meet the T criterion. Based on the current state of knowledge, no specific mode of action is expected for ditolyl ether (neutral organic, narcotic) and the most bioaccumulative isomer (highest BCF) is expected to be the most toxic to aquatic organisms. The proposed testing strategy was accepted. It was agreed that testing of the other isomers and impurities >0.1% that meet the P/vP and B/vB criteria, could be requested in a second substance evaluation decision, depending on the outcome of the tests.

ECHA would like to clarify that the decision concerns six ditolyl ether isomers, i.e. four that were identified by the Registrant as main constituents (2,3'-; 2,4'-; 3,3'- and 3,4'-DTE), and two that were identified as impurities (2,2'- and 4,4'-DTE). It is noted that all constituents >0.1% could be relevant for the PBT assessment. However, it was agreed to remove the request for testing impurities >0.1% in order to follow a less burdensome testing strategy.

Another PfA also suggested to tier the isomer specific toxicity testing. The request was amended and the FELS toxicity test is requested for the individual DTE isomer that leads to the greatest concern and is most likely to meet the T criterion. It should be noted that in the tiered aquatic toxicity testing strategy, the ordering of testing is algae (request 6), daphnia (request 7) and finally fish (request 8), and that ecotoxicity testing is to stop as soon as the DTE isomer that leads to the greatest concern meets, in addition to the (v)P and (v)B criteria, the T criterion. This will minimize the usage of test animals, and vertebrates in particular.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: Fish, Early-life Stage Toxicity Test (test method: OECD TG 210, 2013) for the individual isomer of DTE that is considered (v)P and (v)B and that has the highest BCF as determined in request (5) above. If one of the DTE isomers is already found to meet the criteria for vPvB and/or PBT in accordance with REACH Annex XIII, this request does not need to be addressed. Furthermore, pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall

submit full study reports for the information required under points 1 to 8 of this Section III. Indeed a complete rationale and an access to the whole available information (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation etc.) are needed to fully assess the provided information and to efficiently clarify the concerns. Robust summaries will not be sufficient as each request has specific analytical procedures with individual data points. Data processing, interpretation and transparency are very important in order to fully evaluate the PBT assessment and to compare the isomer specific results.

IV. Deadline

The deadline to provide the information for requests 1, 2, 3, 4 and 5 is set to 36 months. Requests 6, 7 and 8 are to be addressed sequentially in case the outcome of the bioaccumulation test shows that the registered substance, i.e. one or more of the DTE isomers, should be considered bioaccumulative (B) or very bioaccumulative (vB), in addition to being persistent (P) or very persistent (vP), where not meeting the criteria for vPvB in accordance with REACH Annex XIII. In the case the request 6, 7 and 8 are performed, the timeline for performing all requests in the decision is set at 63 months. Based on the PfAs received the number of deadlines was reduced to two and the duration extended because of the introduction of the request for the *Daphnia magna* reproduction test.

V. Adequate identification of the composition of the tested material

In relation to the required experimental studies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the tests must be shared by the Registrant(s).

VI. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/regulations/reach/registration/data-sharing.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the stud(y/ies) on behalf of all of them.

VII. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[7] by Ofelia Bercaru, Head of Unit of Evaluation, on behalf of Leena Ylä-Mononen, Director of Evaluation

Annex:
List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

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