Decision number: CCH-D-2114347445-47-01/F Helsinki, 16 November 2016

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For triisotridecyl phosphite, CAS No 77745-66-5 (EC No 278-758-9), registration number: [redacted]

Addressee [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for triisotridecyl phosphite, CAS No 77745-66-5 (EC No 278-758-9), submitted by [redacted] (Registrant).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 21 July 2016, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 18 July 2013.

On 11 December 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 45 days of the receipt of the draft decision (extension exceptionally granted due to the commenting period falling on the Christmas and New Year period). That draft decision was based on submission number [redacted].

On 24 January 2014 ECHA received comments from the Registrant on the draft decision. The Registrant submitted two spontaneous updates on 14 May 2014 (submission number [redacted]) and on 20 February 2015 (submission number [redacted]).

The compliance check request to submit information to meet the information requirement for Annex X, Section 8.7.3 was removed from the draft decision due to the legislative amendment of this provision by virtue of Commission Regulation (EU) 2015/282 of 20 February 2015. In light of this, ECHA Secretariat did not consider further the Registrant's comments and update concerning this information requirement. ECHA may, in accordance with Article 41 of the REACH Regulation, initiate a further compliance check of the registration dossier with respect to this information requirement.

However, ECHA Secretariat did consider further the Registrant's comments and update(s) concerning the information requirements of Annex I, Section 3, Annex VI, Sections 2.1, 2.3 and 2.3.7, Annex VII, Sections 7.2, 7.5, 8.1, 8.4.1 and 8.5.1, Annex VIII, Sections 8.5.2, 8.1.1, 8.2.1, 8.4.2 and 9.2.2.1, Annex IX, Sections 8.6.2, 8.7.2 and 9.4.2, and Annex X, Sections 9.4.4, 9.4.6, 9.5.1. On the basis of this information and change of scope, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 21 July 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 26 August 2016 ECHA notified the Registrant of the proposal(s) for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal(s) for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposal(s) for amendment received and amended the draft decision.
On 5 September 2016 ECHA referred the draft decision to the Member State Committee.

By 26 September 2016, in accordance to Article 51(5), the Registrant provided comments on the proposal for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 10 October 2016 in a written procedure launched on 29 September 2016.

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

II. Information required

A. Information in the technical dossier related to the identity of the substance

Pursuant to Articles 41(1)(a), 41(3), 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation the Registrant shall submit the following information for the registered substance subject to the present decision:

1. Name or other identifier of the substance (Annex VI, 2.1.);
2. Composition of the substance (Annex VI, 2.3.);
3. Description of the analytical methods (Annex VI, 2.3.7.).

B. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 41(1), 41(3), 10(a)(vi) and (vii), 12(1)(e), 13 and Annexes VII, VIII, IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490) with the registered substance
2. Acute toxicity by inhalation (Annex VIII, 8.5.2.; test method: EU B.2./OECD 403 or OECD 436);
3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;
4. Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route;

Note for consideration by the Registrant:

The Registrant 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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

C. Deadline for submitting the required information

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **23 November 2018**. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

A. Information in the technical dossier related to the identity of the substance

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

1. Name or other identifier of the substance (Annex VI, 2.1)

"Name or other identifier of the substance" is an information requirement as laid down in Annex VI, Section 2.1. of the REACH Regulation. The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore essential parts of substance identification and the cornerstone of all the REACH obligations. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA notes that the Registrant identified the registered substance as of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). The naming of UVCB substances shall consist of two parts: the chemical name and the more detailed description of the manufacturing process. For UVCB substances such as the registered substance, the main identifiers are related to the source of the substance and the specific manufacturing process used. ECHA observes that the Registrant did not provide sufficient information on the manufacturing proces of the substance for its proper identification, as required under Annex VI Section 2.1 of the REACH Regulation.

More specifically, in the updated dossier the Registrant attached details of the manufacturing process including ratio of the starting materials and process parameters. However, the identity and composition of one of the starting materials, namely [redacted] is still ambiguous. The name would suggest that the substance includes all structural isomers of branched tridecyl alcohol, however in section 1.2 of the updated dossier the Registrant provided information that would suggest the presence of other carbon chain lengths in addition to C13, as indicated below in the context of requirement A.2. The Registrant provided also results of chromatographic analyses for "[redacted]", however this information may only demonstrate the UVCB character of this substance, but it does not provide any information about its identity and composition (e.g. C-chain length distribution). This information is crucial to understand the composition of the registered substance as indicated below. Therefore ECHA concludes that the information on the starting materials which determine the composition of the substance and therefore its identity is not sufficiently detailed.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to provide details of the starting materials and the manufacturing processing steps. This must include the following:

- Unambigous identification of the starting materials, including their composition (where appropriate);
- Other process steps and parameters, where relevant.

If the substance covered by the registration, as described above, is manufactured according to different manufacturing processes, including the use of different sources, then the detailed description of the manufacturing process shall be reported separately for each manufacturing process. A manufacturing process may be considered different when the processing steps and/or processing parameters are different.

The Registrant shall ensure that the information is consistent throughout the dossier (and all the identifiers should be consistent).

Regarding how to report the description of the UVCB substance, the information shall be included in the Description field in IUCLID section 1.1, respectively.

Further technical details on how to report the identifiers of UVCB substances in IUCLID are available in paragraphs 2.1 of the Data Submission Manual 18 on the ECHA website.

2. Composition of the substance (Annex VI, 2.3)

"Composition of the substance" is an information requirement as laid down in Annex VI, Section 2.3. of the REACH Regulation. The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA notes that Registrant did not provide sufficient information on the composition of the registered substance.

More specifically, in the updated dossier the Registrant clarified the identity of the main group of constituents, namely "[redacted]", so it refers to the branched [redacted]. However, the identity of this constituent cannot be verified by the analytical data reported in section 1.4, as explained in section A.3. below. Furthermore, ECHA notes that the Registrant included also new additional group of constituents in the composition, namely "[redacted]" with a remark "It is not possible to determine the concentration. It is known that during the manufacture of [redacted]". However, the identity and presence of this group of constituents is not supported by any analytical data.

According to ECHA Guidance chapter 4.3 on the identification and naming of substances under REACH, the Registrant should note that, for UVCB substances such as the registered substance, the following applies:
- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually;
- All known constituents and constituents relevant for the classification and/or PBT assessment of the registered substance shall be reported individually; and
- Unknown constituents shall be identified as far as possible by a generic description of their chemical nature.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to revise the composition of the registered substance providing unambigous information on the identity of its constituents /groups of constituents. If any constituents are present at ≥ 10 % w/w or are relevant for PBT assessment, these shall be reported individually. For each constituent and group of constituents, the minimum, maximum and typical concentration, shall be reported.

The Registrant shall ensure that the information provided on the composition of the substance is confirmed by the required analytical data included in IUCLID section 1.4. More generally, the Registrant shall ensure that the information is consistent throughout the dossier.

Regarding how to report the composition of UVCB substances in IUCLID, this information shall be reported in IUCLID section 1.2. As for UVCB substances there is no differentiation between constituents and impurities, all constituents shall be reported under "Constituents" header in IUCLID section 1.2. Further technical details on how to report the composition of well-defined substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website.

3. Description of the analytical methods (Annex VI, 2.3.7.)

"Description of the analytical methods" is an information requirement as laid down in Annex VI, Section 2.3.7. of the REACH Regulation. Adequate information needs to be present in the technical dossier for the registered substance to meet this information requirement.

ECHA observes that the Registrant has not provided sufficient analytical method that would provide an overview of the composition of the registered substance

More specifically, the Registrant provided in the updated dossier description of the analytical methods used to determine the content of residual alcohol that is sufficient to confirm its content. However, no additional information on how the constituents /groups of constituents of the registered substance were identified is provided. Furthermore, the Registrant has removed the results of GC-MS analysis that was included in the initial dossier and included a statement that "[redacted]."

ECHA concludes that the analytical data included in the updated dossier is not sufficient as it does not allow unambiguous identification of the substance and verification of the composition as reported in section 1.2 of the dossier.

Accordingly, the Registrant is requested to provide description of analytical methods that will confirm the identity and composition of the registered substance. The description of the supportive analysis shall be sufficient for the method to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained. For chromatographic methods, the information shall provide a legible print-out of the chromatogram as well as the report from the chromatographic analysis including the corresponding table of peak assignments that report the w/w (%) of each relevant constituent. individual constituent/group of constituents. In case where the composition of the registered substance cannot be verified by the analytical methods, it can be derived from the composition of the starting material(s) (alcohol), provided that the composition of this starting material(s) is known and supported by the analytical data and details of the calculations are attached in the dossier.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the information derived from the registered substance subject to the present decision: correct description of the methods used to identify and quantify the registered substance as specifically explained in the present decision. The Registrant shall ensure that the information is consistent throughout the dossier.

As for the reporting of the additional analytical data in the dossier, the information should be attached in Section 1.4 of the IUCLID Dossier.

B. Information in the technical dossier derived from the application of Annexes VII to XI

Pursuant to Articles 10(a)(vi) and (vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes VII, VIII, IX, and X of the REACH Regulation.

As already explained in Section III.A.1, above, based on the EC (278-758-9) and CAS (77745-66-5) identifiers and also chemical name provided in the IUPAC name field ("triisotridecyl phosphite"), ECHA understands that the registered substance refers to the UVCB substance consisting of tris(C13-branched alkyl) phosphite constituents for which the alkyl chains are branched at any position. Based on the information contained in the dossier, the registered UVCB substance therefore does not present a defined branching type but instead possibly includes all structural isomers of branched tridecyl phosphites. The information required below shall therefore be submitted on the substance as specified above.

0. Grouping of substances and read-across approach (preliminary considerations)

ECHA based its decision on the evaluation of the registration dossier that contains for the endpoints (Annex VIII, 8.5.2, Annex IX, 8.6.2 and Annex X, 8.7.2) adaptation arguments in form of a grouping and read-across approach under Annex XI, 1.5 of the REACH Regulation. That means that the Registrant considers to achieve compliance with the REACH information requirements for the registered substance [triisotridecyl phosphite] using data of (an) analogue substance(s) [triisodecyl phosphite] (EC No 246-998-3). ECHA has considered first the scientific and regulatory validity of the read-across approach in general before assessing the individual endpoints (sections III.B.1. and III.B.2.).

The Registrant provides the following justification for the read across approach in his updated IUCLID dossier under the endpoint summary "toxicological information":
"Triisodecyl phosphite (TDP) is one of several structurally related alkyl phosphites. Alkyl phosphites are characterized by a phosphorus atom connected to three alkyl ester groups (oxygen connected to an alkyl chain). The closest alkyl phosphite structural analog to TiTDP is triisodecyl phosphite (TDP). The alkyl groups on TDP are branched,C10, isomers and the alkyl groups on TiTDP are branched, C13, isomers. TDP as a data-rich member of this class of phosphites is an important source of analog or read-across data for TiTDP.
These alkyl phosphitesare manufactured using a class of alkyl alcohols that have been well studied and previously accepted as a category (Long Chain Alcohols Category under the OECD SIDS program; Alkyl Alcohols C6 to C13 Category under the U.S. High Production Volume (HPV) program). The category assessment and associated use of read-across data for these alkyl alcohols is particularly relevant for the alkyl phosphites, because these phosphites readily hydrolyze into the associated alcohol used in the manufacture of the phosphite – TDP to isodecanol (C10), TiTDP to isotridecanol (C13). Given this, it appears appropriate to consider both the category approach that was used to assess the alkyl alcohols under REACH as well as the data on the relevant alcohols as analogs to TITDP and the related phosphites".
A matrix comparing TDP data, TiTDP data, and their associated alkyl alcohol data is provided in as separate report in Section 13. For toxicity endpoints where there are corresponding data between TDP and TiTDP – acute oral toxicity, skin irritation, eye irritation, skin sensitisation, in vitro genetic toxicity, in vivo genetic toxicity – the two chemicals have very similar results with the same resulting classifications. Likewise in hydrolysis testing, both TDP and TiTDP showed the ability to rapidly hydrolyse in simulated stomach acid. Given the similarities in toxicities and hydrolytic characteristics plus the established relationship between their corresponding alkyl alcohols, it is appropriate to treat these substances as chemical analogues".

In his update of 20 February 2015 the Registrant provided the following summarized justification for read-across:
"1) TiTDP and TDP are structurally similar chemical analogues in that both are tris alkyl phosphites made with long-chain isoalkyl alcohols.

2) Both substances that have virtually identical toxicity characteristics on endpoints were similar toxicity testing has been conducted. Both substances are:
a. Not acutely toxic via oral route;
b. Non-irritating to the skin and eye using similar testing methods;
c. Negative for genetic toxicity using similar testing methods;
d. Both tested positive for skin sensitisation via the LLNA assay (and both are classified as skin sensitisers).
3) TiTDP and TDP will hydrolyse, both in the environment and upon oral exposure, into their corresponding long-chain alkyl alcohols, isotridecanol (C13) and isodecanol (C10). These long-chain alkyl alcohols are part an existing category that indicates they are structurally similar chemical analogs with similar toxicity. The long-chain alkyl alcohols category was reviewed and approved by the OECD and used in the REACH registration of these alcohols. The fact that the hydrolysis products of TiTDP and TDP are also considered part of a category of chemical analogs provides further support to the treatment of TiTDP and TDP as chemical analogs".

ECHA notes that the justification and documentation provided as to why the properties of the source substances can be read-across to the registered (target) substance fails to meet the requirement of Annex XI, 1.5 that human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). In particular:

- The Registrant merely states that the substances are structurally related. However, the Registrant fails to explain why the difference in chain length of 3 carbon atoms per alkyl chain will not affect the properties of the substance (in sum this accounts for a difference of 9 carbon atoms when comparing triisodecyl phosphite with triisotridecyl phosphite and a difference of 13 C-atoms when comparing phenyl diisodecyl phosphite with triisotridecyl phosphite);

- The Registrant states that the substances are manufactured using a class of alkyl alcohols that have been well studied and previously accepted as categories (OECD SIDS). This justification only compares the starting materials and cleavage products (metabolites) because the SIDS category only relates to the unbound/ free alkyl alcohols.

- The Registrant fails to present any data on the parent compounds; i.e. the phosphites in which the alkyl alcohols/ phenol are bound to phosphorous;

- The Registrant states that "TiTDP and TDP will hydrolyse, both in the environment and upon oral exposure, into their corresponding long-chain alkyl alcohols, isotridecanol (C13) and isodecanol (C10)." ECHA understands that, in principle, the Registrant is arguing that there is only exposure to the hydrolysis products, and not to the parent substance. Consequently, that information on the hydrolysis products will be sufficient to predict the properties of the registered (parent) substance. In this respect it should be noted that some of the hydrolysis rates disclosed in the dossier do not qualify as "rapid" because of half-lives of a few hours to less than one day. Additionally, the Registrant provided hydrolysis tests performed on triisodecyl phosphite (TiDP) and triisotridecyl phosphite (TiTDP) in simulated gastric fluid at 37°C pH 1.2. ECHA considers that (1) with half-lives of 0.4 hours and above, there is still considerable potential for exposure to the parent substance (2) as indicated by the experiments with co-solvent, the hydrolysis of the parent substance does not go to completion in the absence of acetone, and this is explained by lack of solubility of the parent substance.

According to this scheme there would be insoluble (and unreacted) parent substance, and there would therefore be exposure to the parent substance. Therefore, bioavailability of the parent compound and its metabolites cannot be excluded. Indeed, it is assumed that the parent compound is bioavailable (the Registrant states himself that he assumes 50% oral absorption). Consequently, read-across argumentation based on the properties of the hydrolysis products is an inadequate basis to predict the properties of the non-hydrolysed parent substances.

- It is assumed that the hydrolysis of the parent compounds takes place sequentially: cleavage of the first substituent, then cleavage of the second substituent, and finally cleavage of the remaining substituent to yield 3 moles alkyl alcohol and 1 mole phosphate (or 1 mole phenol, 2 moles alkyl alcohol and 1 mole phosphate). This sequential cleavage yields several metabolites which might be bioavailable, and the Registrant does not address the occurrence of intermediate cleavage products. Consequently it is not possible to understand on what basis he predicts their properties.

- The Registrant has proposed that the structural similarity of the substances provides a basis for predicting the properties of the registered substance. Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or this specific case that structural similarity per se is sufficient to enable the prediction of human health properties of a substance, since structural similarity does not always lead to predictable or similar human health properties. Hence, further elements are needed 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 properties that does not underestimate risks. ECHA considers that the requirement of Annex XI, 1.5, that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

- The Registrant has proposed that the similarity in toxicological properties of the registered substance and TiDP provides a basis for predicting the properties of the registered substance. While similarity in 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 toxicological properties per se is sufficient to enable the prediction of human health properties of a substance for a different human health endpoint, since similarity in one toxicological endpoint does not always lead to predictable or similar properties in other toxicological endpoints. Additionally, the number of studies which allow comparison between the two substances are limited (i.e. acute oral, eye and skin irritation, genetic toxicity), and so it is not possible to conclude that this provides a well-founded basis to predict that the toxicological properties of the two substances are indeed similar for the endpoints of Annex VIII, 8.5.2, Annex IX, 8.6.2 and Annex X, 8.7.2. Hence, further elements are needed 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 properties that does not underestimate risks. ECHA considers that the requirement of Annex XI, 1.5, that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach), has not been met.

ECHA notes that in the Registrant's comments to the Member State Competent Authority's proposal for amendment on the read-across approach, the Registrant indicated the possibility to undertake additional testing on uptake and kinetics. Moreover, the Registrant refers to ongoing studies that might be used to further support the read-across approach. ECHA reminds the Registrant that as per the note for consideration in Section IIB above, the Registrant may adapt the testing requested above. Any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

ECHA concludes that the read across adaptation for the endpoints of Annex VIII, 8.5.2, Annex IX, 8.6.2 and Annex X, 8.7.2 cannot be accepted based on the reasons identified above. Additionally, ECHA notes that there are endpoint-specific reasons why the adaptation according to Annex XI, 1.5 is not met, and these are set out in the relevant, individual endpoint related, sections below (sections III.B.1. and III.B.2.).

1. 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 contains negative results for both 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.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. 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).

2. Acute toxicity by inhalation (Annex VIII, 8.5.2.)

"Acute toxicity by the inhalation" is a standard information requirement as laid down in Annex VIII, Section 8.5.2. 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. As outlined in column 2 of Annex VIII, Section 8.5 of the REACH Regulation "in addition to the oral route (8.5.1), for substances other than gases, the information mentioned under 8.5.2 and 8.5.3 shall be provided for at least one other route. The choice for the second route will depend on the nature of the substance and the likely route of human exposure".

The Registrant has sought to adapt the information requirements of Annex VIII, Section 8.5.2 and 8.5.3 of the REACH Regulation by means of a read-across approach between the registered substance and the source substance, trisisodecyl phosphite.

As explained in section III.B.0 above, ECHA concludes that the read-across justification as provided by the Registrant cannot be accepted as a valid adaptation to the information requirements. Furthermore, the Registrant did not provide any information on the registered substance itself. Consequently there is an information gap and it is necessary to provide information for at least one of the standard information requirements.

In light of the properties of the substance provided by the Registrant under the toxicokinetic section, i.e. no dermal absorption, and the information provided on the uses and human exposure, i.e. uses with spray application, ECHA considers that testing by the inhalation route is most appropriate.

In his updated dossier the Registrant has provided the following waiver for acute toxicity by inhalation: *"In accordance with column 2 of REACH Annex VIII section 8.5.2, acute toxicity testing via the inhalation route is appropriate if exposure of humans via inhalation is likely. TiTDP is predicted to have a low vapour pressure (0.00000114 Pa; EPISUITE) and the chemical safety assessment shows that exposure to aerosols or droplets of inhalable size is unlikely under normal use conditions. In addition, there were no signs of systemic toxicity in an acute oral toxicity study performed with TiTDP. There were also no signs of systemic toxicity in acute oral toxicity, acute dermal toxicity and acute inhalation toxicity studies of the structural analogue, used in a read-across approach".*

ECHA notes that there may be exposure of humans via the inhalation route (PROC 7: industrial spraying and PROC 10: roller application or brushing) as indicated in IUCLID dossier and the CSR. These two PROCs would indicate the production of droplets, which ECHA assumes are of inhalable size, as no evidence is provided to the contrary. ECHA also notes that RCRs of [redacted] and [redacted] are provided for PROCs 7 and 10, respectively, by the inhalation route. ECHA therefore considers that exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size. ECHA considers that the absence of acute oral toxicity is not a valid adaptation of the information requirement according to column 2 or Annex XI. ECHA has rejected the read-across to the structural analogue as set out in III.B.0. above, and no valid adaptation by column 2 or Annex XI is therefore available.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Acute inhalation toxicity (test method: EU B.2./OECD 403 or OECD 436).

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, 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.

In the dossier the Registrant has not provided any study record of a sub-chronic toxicity study (90-day) carried out with the registered substance that would meet the information requirement of Annex IX, Section 8.6.2. Instead, the Registrant has sought to adapt this information requirement by providing a read-across study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422) source substance, trisisodecyl phosphite.

As explained under section III.B.0 above, ECHA concludes that the read-across justification as provided by the Registrant cannot be accepted as a valid adaptation to the information requirements.

Additionally, ECHA reminds that according to REACH Annex IX, section 8.6.2. a 90-day study in one species, rodent, male and female is a standard information requirement unless the column 2 adaptation applies. ECHA notes that the Registrant has provided an OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) study extended with dosing of F0 females through Day 21 of lactation (total of 8-9 weeks) performed with a read-across substance (Triisodecyl phosphite, EC 246-998-3). ECHA considers that the enhanced OECD TG 422 with a read-across substance does not meet the requirements of Annex XI, 1.5 because

- The male rats were treated only for 28 days and the female rats for 8-9 weeks (56 days in the CSR), and hence the exposure duration is less than 90 days as indicated in the OECD TG 408, and so this does not meet the requirement that the proposed test cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.
- Many of the observations and examinations performed were done already at day 28 and in one species (males) only. Hence this fails the requirement that the proposed study have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

These are additional reasons why the adaptation according to Annex XI, 1.5 is rejected. For all o the above reasons, the adaptation of the information requirement is rejected.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

In light of the physico-chemical properties of the substance liquid with low vapour pressure and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

According to the test method EU B.26/OECD 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, the Registrant is 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 408) in rats.

4. Pre-natal developmental toxicity study (Annex X, 8.7.2.)

A "pre-natal developmental toxicity study" 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.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2. Instead, the Registrant has sought to adapt this information requirement by providing a read-across study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422) with the source substance, trisisodecyl phsophite.

As explained under section III.B.0 above, ECHA concludes that the read-across justification as provided by the Registrant cannot be accepted as a valid adaptation to the information requirements. In addition, the OECD 422 study using the read-across approach does not fulfil the adaptation requirements of Annex XI, 1.5. of the REACH Regulation because the results have no adequate and reliable coverage of the key parameters . Specifically, ECHA notes that an OECD TG 422 screening test does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. The read-across adaptation fails for all the reasons given above. 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 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

In his dossier update the Registrant stated that "*According to Annex IX, section 8.7.3, column 2 of Regulation No. 1907/2006, a pre-natal developmental toxicity study need not be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via the relevant route of exposure and there is no or no significant human exposure [...]. A Justification for read across to TDP is provided in IUCLID Section 13".*

However, the Registrant himself indicated that there is potential for oral and inhalation absorption: "*There are no specific toxicokinetic studies of TiTDP, but based on its extremely high log Kow (>16), it's extremely low water solubility, and it's high molecular weight (629.05) it is expected to have limited dermal absorption potential and moderate oral and inhalation absorption potential".* Thus the Registrant has not demonstrated that there is no systemic absorption. Additionally, the Registrant has shown RCRs above 0.1 in his CSR, and so ECHA considers that the requirement for no or no significant human exposure is not met. The Registrant has failed to meet the criteria of the adaptation.
Hence, the adaptation of the information requirement is rejected.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rats or rabbits by the oral route.

Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that no study on a second species is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2.

C. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also contained a two-generation reproductive toxicity study (EU B.35, OECD TG 416) or an extended one-generation reproductive toxicity study (EU B.56, OECD TG 443) (Annex X, Section 8.7.3.) , and requests for information on Melting/freezing point (Annex VII, 7.2.), Vapour pressure (Annex VII, 7.5.), Acute toxicity by oral route (Annex VII, 8.5.1.), Skin irritation or skin corrosion (Annex VII, 8.1.), *In vivo* skin irritation (Annex VIII, 8.1.1.), Eye irritation (Annex VII, 8.2.), *In vivo* eye irritation (Annex VIII, 8.2.1.), *In vitro* gene mutation study in bacteria (Annex VII, 8.4.1.), *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2.), Hydrolysis as a function o pH (Annex VIII, 9.2.2.1.), Long term toxicity testing on terrestrial invertebrates (Annex X, 9.4.4.), Effects on soil micro-organisms (Annex IX, 9.4.2.), Long term toxicity testing on plants (Annex X, 9.4.6.), long term toxicity to sediment organisms (Annex X, 9.5.1.), and the environmental hazard assessment (Annex I, 3). As these studies are not addressed in the present decision, ECHA Secretariat considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 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 ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation, E3.

[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.