ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 20 November 2018

Addressee
[redacted]

Decision number
CCH-D-2114449719-33-01/F

Registered substance subject to this decision, hereafter 'the Substance'
Ethyltriphenylfosfonium bromide
EC number: 216-223-3
CAS number: 1530-32-1

Your registration
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11/12/2015
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information generated with a test material representative of the Substance on:

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.);**
   - **Identification and quantification of the main constituent(s)**
2. **Description of the analytical methods (Annex VI, Section 2.3.7.);**
   - **Identification and quantification of the counter-ion**
3. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471);**
4. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487);**
5. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490); provided that both studies requested under 3. and 4. have negative results;**
6. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.;**

test method: OECD TG 408) in rats;

7. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route.**

You are required to submit the requested information in an updated registration dossier by ***27 November 2020***.

You are required to submit the results in a form of a robust study summary[1]. You shall also update the chemical safety report. The timeline has been set to allow for sequential testing.

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

The scope of this compliance check decision is limited to the standard information requirements of Annex VI, Section 2 to the REACH Regulation and standard toxicological information requirements of Annex VIII to the REACH Regulation.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[2] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] See ECHA Practical guide 3: https://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf/
[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

SUBSTANCE IDENTITY INFORMATION

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

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)**

"High-pressure liquid chromatogram or gas chromatogram" is an information requirement as laid down in Annex VI, Section 2.3.6. of the REACH Regulation. Adequate information needs to be present in the technical dossier to meet this requirement.

The gas chromatography analysis (GC-MS/MS) (file name [redacted]) attached in IUCLID section 1.4 includes a chromatogram on page 2 which shows two peaks identified with the same CAS number 1530-32-1 (table on page 1), which is the CAS used as one of identifiers of the Substance. Only one peak (with retention time 7.36) has been quantified with an area%= 99.12%. Other 2 chromatograms are included on page 3 and are labelled "for stability study".

The substance has been identified as a mono-constituent substance, and the main constituent "[redacted]" has been reported with a typical concentration of [redacted]% in IUCLID section 1.2.

From the information available in section 1.4, it appears that the GC-MS/MS has been used to determine the composition of the substance. However, it is not clear how the GC-MS/MS results (table on page 1) have been used because no further explanation has been provided on why two peaks, with different retention times, have been identified with the same CAS entry, and would correspond to a mono-constituent substance. In addition it is not clear the purpose of the two chromatograms reported on page 3. The retention times are not the same as for the chromatogram on page 2, but there is no indication of a different method used for such chromatograms, and therefore the correlation between this data and the identification of the substance is not self-evident.

Therefore, you will need to explain how the results of the gas chromatography have been used to determine the composition of the Substance as reported in IUCLID 1.2.

You shall provide this information in IUCLID section 1.4.

In your comments to the draft decision, you agreed to perform this study.

2. **Description of the analytical methods (Annex VI, Section 2.3.7.)**

The description of analytical methods or appropriate bibliographical reference for the identification of the substance is a formal information requirement of Annex VI Section 2.3.7.
You have identified your Substance with EC name "ethyltriphenylfosfonium bromide", which indicates that Br is present as a counter-ion in your Substance. However you have not

provided a description of the analytical methods used to identify and quantify the Br counter-ion.

Therefore, your dossier does not have sufficient information to establish the identity of the Substance.

Accordingly, you are required to provide the description of the analytical method for the identification of the Br counter-ion.

The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

You shall provide this information in IUCLID section 1.4.

In your comments to the draft decision, you agreed to perform this study.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for the endpoints addressed in this Decision (point 3, 4, 5, 6, and 7), adaptation arguments either in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation and/or of predictions generated with the use of QSAR models under Annex XI, Section 1.3 of the REACH Regulation. ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

1. For the use of read-across approach according to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Unambiguous substance identity for both the source substance and the target substance is therefore a prerequisite for a read-across assessment. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data on reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

   Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[3]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/

[3] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case. Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

2. For the use of adaptations using Weight of Evidence (WoE), according to Annex XI, Section 1.2., it is required that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion. Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the Substance with respect to the specific standard information requirement.

3. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

For your registration an *In vitro* gene mutation study in bacteria is a standard information requirement.

You have indicated "(Q)SAR" in the administrative section of one endpoint study record in the technical dossier for "in vitro gene mutation in bacteria". In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox and it is indicated within this report that it is used to predict gene mutation for the Substance based on read-across.

ECHA notes that:

1. You have not provided an assessment to address structural similarity/dissimilarity between the Substance and the proposed analogue(s).
2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the Substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across

You have further provided within the Endpoint Study Summary for "Genetic Toxicity in vitro" an indication that you consider the information you provided in the Endpoint Study Records for Genetic Toxicity in vitro in a Weight of Evidence Approach.

ECHA notes that, for the reasons explained above, the information provided do not constitute relevant and reliable information in the context of a weight of evidence approach.

ECHA therefore concludes that:

- The proposed adaptation is not in line neither with the conditions specified in Annex XI, Section 1.5., nor with those specified in Annex XI, Section 1.2. and is therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

In your comments to the draft decision, you agreed to perform this study.

4. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

For your registration, an *In vitro* cytogenicity study in mammalian cells or in vitro micronucleus study in a standard information requirement.

You have indicated "(Q)SAR" in the administrative section of the endpoint study record in the technical dossier for "in vitro cytogenicity / chromosome aberration study in mammalian cells". In the technical dossier you provided an automated report generated with the OECD QSAR Toolbox and it is indicated within this report that it is used to predict chromosome aberration for the Substance based on read-across.

ECHA notes that:

1. You have not provided an assessment to address structural similarity/dissimilarity between the Substance and the proposed analogue(s).
2. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance.
3. You have not provided any experimental studies neither with the Substance nor with structurally similar analogue(s) which would substantiate the prediction. Absence of experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across.

You have further provided within the Endpoint Study Summary for "Genetic Toxicity in vitro" an indication that you consider the information you provided in the Endpoint Study Records for Genetic Toxicity in vitro in a Weight of Evidence Approach.

ECHA notes that, for the reasons explained above, the information provided do not constitute relevant and reliable information in the context of a weight of evidence approach.

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- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

In your comments to the draft decision, you agreed to perform this study.

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

For your registration an *In vitro* gene mutation study in mammalian cells is a standard information requirement if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained. Currently your dossier does not have acceptable information on the two endpoints mentioned above. Adequate information on *in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the Substance to meet this information requirement provided that both studies requested under 1 and 2 have negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

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.

In your comments to the draft decision, you indicated that the requested study is already available and updated within the dossier. However, no experimental study according to OECD TG 476 or TG 490 has been reported for this endpoint in the current registration dossier with submission number [redacted] As indicated in the notification of the draft decision to you, no dossier update will be taken into account by ECHA for the ongoing decision making process.

6. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

For your registration a Sub-chronic toxicity study (90 day) is a standard information requirement.

You have indicated "read-across based on grouping of substances (category approach)" in the administrative section of the endpoint study record for "Repeated-dose toxicity" (oral route). You provided an automated report generated with the OECD QSAR Toolbox and it is indicated within this report that it is used to predict Repeated Dose Toxicity, LOEL, NOEL for the Substance based on read-across. You also claimed read-across to tetrakis(hydroxymethyl)phosphonium chloride (CAS No: 124-64-1 / EC No: 204-707-7) for this endpoint quoting National Toxicology Programme study report as the source of information.

You have further provided a document entitled "[redacted]" that contains categorisation/read-across apporach for the Substance (the target substance) with the use of the functionalities by the QSAR Toolbox and other modeling software. You have identified the following substances as analogues (source substances) for use of read-across across on the basis of common functional groups identified by the modelling software:

- tetrakis(hydroxymethyl)phosphonium chloride CAS No: 124-64-1
- benzyltriphenylphosphonium chloride CAS No: 1100-88-5

- ethyltriphenylphosphonium iodide CAS No: 4736-60-1

You summarised the experimental study for CAS No: 124-64-1 and the automated generated predictions with the OECD QSAR Toolbox mentioned above to support the hypothesis for similar toxicity for Repeated-dose toxicity.

ECHA notes that:

1. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance for the information provided within the OECD QSAR Toolbox report;
2. You have not provided an assessment to address structural similarity/dissimilarity between the target and the source substances for the predictions / read-across proposals as presented within the automated OECD QSAR Toolbox reports;
3. You have not provided an assessment to address structural dissimilarity between the target and the source substances for the read-across proposal as presented in the category justification document. The target substance contains phenyl groups compared to the source substance for which you provided an experimental study; and
4. You have not provided experimental studies neither with the target substance nor with a structurally similar source substance which would substantiate the prediction for the information requirement of a sub-chronic toxicity study. You have not provided any experimental study for Repeated-dose toxicity with the substances you proposed as analogues (source substances), benzyltriphenylphosphonium chloride and ethyltriphenylphosphonium iodide. Absence of relevant experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across.

You have further provided within the Endpoint Study Summary for "Repeated dose toxicity" an indication that you consider the information you provided in the Endpoint Study Records for Repeated-dose toxicity (oral route) in a Weight of Evidence Approach.

ECHA notes that the information provided as explained above, does not constitute relevant and reliable information in the context of a weight of evidence approach.
ECHA therefore concludes that:

- The proposed adaptation complies neither with the conditions specified in Annex XI, Section 1.5., nor with those specified in Annex XI, Section 1.2.,and is therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

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

In your comments to the draft decision, you indicate that an OECD TG 422 study is available and will be updated for this endpoint. You indicated in your comments that you consider that the results obtained in a combined repeated dose toxicity study with reproduction/developmental toxicity screening test warrant classification of the Substance as STOT RE 2. According to the provisions of Annex IX, 8.6.2, Column 2, a sub-chronic (90-day) toxicity study does not need to be performed if the substance is classified as STOT RE 1 or 2. ECHA notes that the Substance is currently neither subject to a harmonised classification for this hazard nor to a self-classification from your initiative. Therefore, in the absence of classification as STOT RE, there is a data gap for the information requirement of Annex IX, 8.6.2 for a sub-chronic (90-day) toxicity study.

Furthermore, ECHA highlights that the combined repeated dose toxicity study with reproduction/developmental toxicity screening test as described in the OECD TG 422 does not provide the information required by Annex IX, Section 8.6.2., because the exposure duration is less than 90 days and the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408).

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

For your registration a pre-natal developmental toxicity study in a first species is a standard information requirement.

You provided an automated report generated with the OECD QSAR Toolbox indicating that is used to predict LOEL for the Substance based on read-across for Developmental toxicity.

You also claimed read-across to tetrakis(hydroxymethyl)phosphonium chloride (CAS No: 124-64-1 / EC No: 204-707-7) for this endpoint. You provided a pre-natal developental toxicity study (OECD TG 414) and a range finding study with this source substance, quoting NTIS study report as source of information.

You have further provided a document entitled "[redacted]" that contains categorisation/read-across apporach for the Substance (the target substance) with the use of the functionalities by the QSAR Toolbox and other modeling software. You have identified the following substances as analogues (source substances) for use of read-across across on the basis of common functional groups identified by the modelling software:

- tetrakis(hydroxymethyl)phosphonium chloride CAS No: 124-64-1
- benzyltriphenylphosphonium chloride CAS No: 1100-88-5
- ethyltriphenylphosphonium iodide CAS No: 4736-60-1

You summarised the experimental study for CAS No: 124-64-1 and the automated generated prediction with the OECD QSAR Toolbox mentioned above to support the hypothesis for similar toxicity for Pre-natal developmental toxicity.

ECHA notes that:

1. You have not provided any read-across hypothesis establishing why the results generated with the source substance can be used to predict the results for the target substance for the information provided within the OECD QSAR Toolbox report;

2. You have not provided an assessment to address structural similarity/dissimilarity between the target and the source substances for the predictions / read-across proposals as presented within the automated OECD QSAR Toolbox reports;
3. You have not provided an assessment to address structural dissimilarity between the target and the source substances for the read-across proposal as presented in the category justification document. The target substance contains phenyl groups compared to the source substance for which you provided an experimental study; and
4. You have not provided experimental studies neither with the target substance nor with a structurally similar source substance which would substantiate the prediction for the information requirement of a sub-chronic toxicity study. You have not provided any experimental study for Pre-natal developmental toxicity with the substances you proposed as analogues (source substances), benzyltriphenylphosphonium chloride and ethyltriphenylphosphonium iodide. Absence of relevant experimental data to substantiate the hypothesis for the prediction makes any adaptation based on read-across invalid as it does not allow a comparative assessment of properties of the source and target substance and hence concluding whether properties could be read across.

You have further provided within the Endpoint Study Summary for "Toxicity to Reproduction" an indication that you consider the information you provided in the Endpoint Study Records for Pre-natal developmental toxicity in a Weight of Evidence Approach.

ECHA notes that the information provided as explained above, does not constitute relevant and reliable information in the context of a weight of evidence approach.

ECHA therefore concludes that:

- The proposed adaptation is not in line neither with the conditions specified in Annex XI, Section 1.5., nor with those specified in Annex XI, Section 1.2.,and is therefore rejected.
- Contrary to Article 3(28) of the REACH Regulation, the documentation of the endpoint study records is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision, you indicate that an OECD TG 422 study is available and will be updated for this endpoint. You indicated in your comments that you consider that the results obtained in a combined repeated dose toxicity study with reproduction/developmental toxicity screening test warrant classification of the Substance as Repro 2. According to the provisions of Annex IX, 8.7, Column 2, a pre-natal developmental toxicity study does not need to be performed if the substance is classified as

Repro 1A or 1B: may damage the unborn child. ECHA points out that classification as Repro 2 does not constitute a valid adaptation of the information requirement of Annex IX, 8.7.2 according to the provision of Annex IX, 8.7, column 2. Furthermore, ECHA stresses that the registered substance is currently neither subject to a harmonized classification for this hazard nor to a self-classification from your initiative.

Therefore, there is a data gap for the information requirement of Annex IX, 8.7.2 for a pre-natal developmental toxicity study.

ECHA also highlights that the combined repeated dose toxicity study with reproduction/developmental toxicity screening test as described in the OECD TG 422 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 like examinations of foetuses for skeletal and visceral alterations

Appendix 2: Procedural history

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

The compliance check was initiated on 16 January 2018.

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

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

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

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

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

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