~~Confidential~~

Helsinki, 18 August 2022

Addressees
Registrant(s) of JS_1530-32-1_[redacted] as listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject to this decision
22 June 2021

Registered substance subject to this decision ("the Substance")
Substance name: Ethyltriphenylfosfonium bromide
EC number: 216-223-3

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By the decision of 20 November 2018 ("the original decision") ECHA requested you to submit information by 27 November 2020 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration dossier specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

A. Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490);

B. Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats.

You are therefore still required to provide this information requested in the original decision.

Reasons for the requests are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VIII to IX of REACH", respectively.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[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 A: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

You were requested to submit information derived with the registered substance for In vitro gene mutation study in mammalian cells if studies according to OECD TG 471 and 473 with the Substance showed negative results.

ECHA notes that you have provided studies according to OECD TG 471 and 473, respectively, with negative results.

In response, you provided: an in vitro gene mutation study in mammalian cells according to OECD TG 476 (2015).

We have reviewed this information and identified the following issue(s):

1. Study not adequate
To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490[3]. The key parameter(s) of these test guidelines include:

a) Positive control substance(s) must be included in the study for cultures with and without metabolic activation, respectively. The positive control substance(s) must produce a statistically significant increase in the response compared with the concurrent negative control.

However, the reported data for the study you have provided do not include a positive control for cultures with metabolic activation (in this case 7,12-dimethylbenzanthracene) that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative for cultures.

The information provided does not cover key a parameter required by OECD TG 476.

2. Study not performed according to GLP
Moreover, toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided study was indicated as "not specified" for GLP.

The laboratory where the study was performed ([redacted]) did not hold a GLP certificate in 2014-2015 when the study was performed.

Based on the above, the information you provided does not fulfil the information requirement and you are still required to provide In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490).

In your comments to the draft decision you indicate that a study is underway. ECHA acknowledges this information, but in the absence of information cannot perform an evaluation.

[3] ECHA Guidance R.7a, Table R.7.7–2, p.557

Appendix B: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

You were requested to submit information derived with the registered substance for a sub-chronic toxicity study (90-day).

In response, you provided short-term toxicity study (28-day) (2020) and an adaptation according to Column 2 of Annex IX, Section 8.6.2.:

We have reviewed this information and identified the following issue(s):

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil the following criterion:

- a reliable short-term toxicity study (28-day) is available and shows severe toxicity effects meeting the criteria for classifying the substance as STOT RE (category 1 or 2), and where the NOAEL-90 days can be extrapolated for the same route of exposure.

You stated that "*a sub-chronic toxicity study (90 days) does not need to be conducted because a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the relevant criteria for classifying the substance, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure*"

The short-term toxicity study (28-day) you provided demonstrated similar types and frequencies of the observed liver lesions in exposed animals and in the control group. According to your IUCLID file, sinusioidal haemorrhage was recorded in 2 control animals and in 2 exposed animals in the high dose group. Foci of centrilobular/periportal necrosis/inflammation were recorded in 4 control animals and in 5 exposed animals in the high dose group.

Therefore, the liver lesions have not been demonstrated to be exposure-related, and the derived NOAEL-90-days cannot be considered reliable. Consequently the classification to STOT RE is not reliable and your adaptation is rejected.

In your comments to the draft decision you agree that the short-term toxicity study cannot be used for classification, and you propose instead to classify for STOT RE 2 based on a dose-range finder study.

According to CLP Annex I, 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class.

Thus, it has to be evaluated whether the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity. One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity then it could be considered to be a repeated-dose effect distinct from the acute toxicity (ECHA guidance on the application of the CLP criteria Section 3.9.2.5.1.).

In your dose-range finder study for the OECD TG 407 study mortality was recorded at an exposure of 200 mg/kg bw/day, while the acute oral LD50 value of test chemical was considered in between 50-300 mg/kg body weight for your Substance.

It is the opinion of ECHA that the mortality recorded in the DRF study occurred at exposure levels which are close to those causing acute toxicity. For that reason the mortality is not regarded as true repeated dose toxicity and cannot be used for STOT RE classification.

Therefore, the information requirement is not fulfilled.

Based on the above, the information you provided does not fulfil the information requirement and you are still required to provide a sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[4].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix D: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 20 November 2018 ("the original decision"). Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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

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

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[9]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you at the time of the original ECHA decision
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.