~~Confidential~~

Helsinki, 14 March 2022

Addressees
Registrant(s) of JS_126-71-6 as listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject to this decision
28 August 2019

Registered substance subject to this decision ("the Substance")
Substance name: Triisobutyl phosphate
EC number: 204-798-3

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 25 April 2018 ("the original decision") ECHA requested you to submit information by 2 May 2019 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):

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance.**

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

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex IX of REACH".

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 IX of REACH

1. Pre-natal developmental toxicity study in a second species

You were requested to provide a pre-natal developmental toxicity (PNDT) study (Annex IX, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance ('the Substance').

You have provided an OECD TG 414 study (2019) conducted using rabbits as a second species. We have assessed the provided information and identified the following issue(s):

Dose level selection

To be considered compliant and enable concluding whether the Substance has dangerous properties, a study has to meet the requirements of OECD TG 414.

With regard to dose selection, OECD TG 414 states that "*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering.*"

In addition, the study has to be adequate for the purpose of classification and labelling as stated in Annex I, Section 1.0.1. of REACH, *"the objectives of the human health hazard assessment shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008"* (the CLP Regulation).

In the provided OECD TG 414 study:

- The doses used were 15, 50, and 150 mg/kg bw/day
- Animals were exposed during gestations days (GD) 6-28
- No maternal or developmental toxicity was observed, and the maternal and developmental NOAELs were set to 150 mg/kg bw/day based on the absence of adverse effects.

The dose selection for the provided OECD TG 414 study was based on a dose range finding (DRF) study in pregnant rabbits exposed during GD 6-28, using doses of 0, 100 and 300 mg/kg bw/day.

You explain that '*the effects observed at 300 mg/kg/day in the dose range finder in pregnant rabbits were considered too severe, in particular during the first days of treatment (mean body weight loss of 4% together with severely reduced/almost absent relative food intake over Days 6-9 post-coitum), without a complete recovery at the end of the treatment period as body weight gain and food consumption remained lower than control values during the entire study period.*' Therefore, the highest dose in the main OECD TG 414 study was set to 150 mg/kg bw/day.

In the provided OECD TG 414 study no maternal or developmental toxicity were reported at 150 mg/kg bw/d, the highest dose tested. Therefore, ECHA has evaluated if it can be demonstrated that the highest dose was chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight).

The dose level selection for the OECD TG 414 study was based on the DRF study. The duration and test species in the DRF study were comparable to the main OECD TG 414 study and hence the DRF study provides relevant information. The DRF used dose levels of 0, 100 and 300 mg/kg bw/day. The results reported reduced food consumption and reduced body weights in the treated animals compared to controls.

In the DRF study, clinical signs reported reduced faeces production not only in the treated animals but also in 3/5 control animals. ECHA acknowledges that when compared to controls, at 300 mg/kg bw/day there was a transient severely reduced relative food intake (-91%) and body weight loss (4%) on GD 6-9, with partial recovery thereafter. At the end of treatment, when compared to controls, terminal body weight in females at the 100 and 300 mg/kg bw/day groups were 2.5% and 7% lower, respectively. As the body weights of treated dams were only slightly lower than controls, and there were no clinical signs of toxicity attributed to the administration of the Substance, ECHA considers that the effects observed at 300 mg/kg bw/day in the DRF study indicate some toxicity, but not severe suffering.

Therefore, using half of that dose (150 mg/kg bw/day) as the highest dose tested in the main OECD TG 414 study cannot be justified, and the aim '*to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but no death or severe suffering*' has not been shown.

Consequently, the dose level selection was too low. The study does not fulfil the key parameter set in OECD TG 414 and it is not compliant.

ECHA notes that currently, due to too low dose level selection, the study does not allow to conclude whether the Substance has dangerous properties and therefore no conclusion on classification and labelling for developmental toxicity in accordance with the CLP Regulation can be made, as adverse effects on the tested parameters at higher doses cannot be excluded. Therefore, the study is inconclusive for hazard assessment.

Conclusions

The original decision requested you to provide a study according to the OECD TG 414.

Taken together the results of the DRF study and the main OECD TG 414 study, ECHA considers that the dose levels in the main OECD TG 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, i.e. with "*the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*".

In your comments to the draft decision you provide details on the two DRF studies on which the dose selection of your OECD TG 414 study was made. You conclude that the dose selection for the main study was in particular based on the decrease in maternal body weight gain which was decreased by 34% at 100 mg/kg bw/day and by 57% at 300 mg/kg bw/day compared to controls in the DRF study. You compare these effects with a recent ECETOC publication which indicates that a 20% decrease in maternal body weight gain could be judged as exceeding the maximum tolerated dose (MTD).

However, as already stated above, ECHA notes that at the end of treatment, the body weights of treated dams were only slightly lower than controls, and there were no clinical signs of toxicity attributed to the administration of the Substance. Therefore, ECHA retains its view that the effects observed at 300 mg/kg bw/day in the DRF study indicate some toxicity, but not severe suffering.

Taken together the information on the DRF studies you provided with your comments is mostly identical to the already provided information in the registration dossier, and it does not change the conclusion that too low dose levels were selected for the OECD TG 414 study.

In your comments you also agree that the high dose in the main study might have been too low as unexpectedly no maternal or developmental toxicity was observed.

Therefore the provided study is not compliant.

Based on the above, the information you provided does not fulfil the information requirement and you are still required to provide a pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance.

In your comments you consider that testing of a dose level higher than 150 mg/kg bw/day could be justified, but conclude that an additional higher dose is limited to a level below a factor of two above the already tested dose level of 150 mg/kg bw/day. For that reason you propose to conduct a supplementary oral OECD TG 414 study in rabbits with a reduced number of dose groups (i.e. control group + high-dose group).

ECHA understands that you intend to adapt the currently incompliant information requirement according to Annex XI 1.2 (Weight of evidence) by using a combination of data from the study already performed and a new study testing a suitable high dose which complies with OECD TG 414, paragraph 14.

ECHA notes that the weight of evidence approach you propose in your comments appears generally plausible. However, any adaptation must fulfil the specific rules outlined in Annexes VII to X or the general rules of adaptations specified in Annex XI to the REACH Regulation. Once the dossier has been updated, ECHA will then evaluate whether the submitted information (study or adaptation) complies with the information requirement addressed in this decision.

Appendix B: 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[3].

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[4].

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

Appendix C: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 25 April 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 40 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 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 adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[5] 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)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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[8]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[8] 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 E: 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
[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.