EUROPEAN CHEMICALS AGENCY

Helsinki, 23 August 2018

Addressee: [redacted]

Decision number: CCH-D-2114439296-43-01/F
Substance name: 2,4,8,10-tetra(tert-butyl)-6-hydroxy-12H-dibenzo[d,g][1,3,2]dioxaphosphocin 6-oxide, sodium salt
EC number: 286-344-4
CAS number: 85209-91-2
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 27 September 2017

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

By decision TPE-D-2114343940-51-01/F of 20 September 2016 ("the original decision") ECHA requested you to submit information by 27 September 2017 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 update specified in the header above, and concludes that:

Your registration still does not comply with the information requirement for pre-natal developmental toxicity (Annex IX, Section 8.7.2) and ECHA requests you to submit the following information:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (Wistar rat), oral route (gavage)

You have to submit the requested information in an updated registration dossier by ***30 August 2019***. You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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 IX, Section 8.7.2. 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, shall 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[1] by Kevin Pollard, Head of Unit E1

[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.

Appendix 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100-1000 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.

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

In decision TPE-D-2114343940-51-01/F ("the original decision") you were requested to submit information derived with the registered substance for a pre-natal developmental toxicity study for a first species (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

In the updated registration, you did not provide a study according to OECD 414. Instead, you provided in the IUCLID section for developmental toxicity a study according to test guideline OECD 416 (Two-generation reproduction toxicity study) performed with Wistar rats and dietary dosing of 1000, 3000 and 10000 ppm (F0 generation) and 1000 and 3000 ppm (F1 generation) of the registered substance. ECHA notes that at the time of the original decision the OECD 416 study was already ongoing for regulatory purposes other than REACH and was consequently not addressed in the original decision. You have now given the following arguments why, based on this OECD 416 study, a pre-natal developmental toxicity study is not needed:

1. You state that "*In the frame of the 2-generation reproduction toxicity study possible skeletal and visceral malformations of foetuses were not investigated. Instead development of pups of the F0 parental generation was followed until pairing of this F1 generation to produce the F2 generation. Development of pups of the F2 generation was followed until Day 21 of lactation. No differences to control animals were observed. This finding of no developmental effects was taken as clear indication that skeletal and visceral malformations did not occur in embryos / pups of the F1 and F2 generation.*"
2. You further state that "*Based on the results of this 2-generation reproduction toxicity study it is concluded that there is sufficient evidence that exposure of pregnant female rats to the test substance at dose levels up to 3000 ppm in diet (corresponding to 230-286 mg/kg body weight/day) did not produce developmental toxicity. Therefore, no further testing of developmental toxicity / teratogenicity is needed.*"
3. You conclude that the most serious effect observed in the high dose group of the two-generation reproduction toxicity study was absence of offspring. Based on your assessment of the various reproductive parameters analysed in the study you conclude that "*these findings were indicative for (early) embryonal loss*" as the reason for absence of offspring in the high dose group. Based on the strong antimicrobial activity of the test substance and the strong depression of the food conversion ratio observed in high dose animals you further concluded that "*disturbance of the gut microbiota is very likely. Disturbance of the gut microbiota is known to lead to specific dietary deficiencies and/or malnutrition. Based on these considerations it is rather likely that the reason for loss of implantations in high dose females was malnutrition and/or dietary deficiencies resulting from disturbance of the gut microbiota by the antimicrobial activity of the test substance. No toxic effects and no effects on reproduction were observed in animals of the mid*

and low dose groups (3000 ppm and 1000 ppm) resulting in the NOAEL derived at 3000 ppm. The effect observed on reproduction in high dose animals is considered a secondary effect and not primary reproduction toxicity of the test substance"

ECHA notes the following concerning the above arguments:

1. You state already in your argument that malformations of foetuses were not investigated. As already concluded as regards OECD 421 and 416 studies in the original decision "*those studies do not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations. Moreover, due to the natural delivery in the screening study and a two-generation reproductive toxicity study, malformed offsprings are usually cannibalised by the dams and remain undetected.*" I.e. an OECD 416 does not provide information on malformations unlike an OECD 414 study were dams are sacrificed before delivery and foetuses are examined without a possibility of the dams to cannibalise the malformed new-borns before they are identified.
2. In addition to the above generic arguments concerning the limitations of the design of the OECD 416 test guideline study and full information on developmental toxicity provided by an OECD 414 study for the provision of information requirement of Annex IX, Section 8.7.2. (point 1), ECHA notes that the OECD 416 study you provided does not provide any information on possible developmental toxicity above 3000 ppm (corresponding to 230-286 mg/kg body weight/day) due to the absence of offspring above that dose.
3. Your claim concerning the absence of offspring in the high dose group of this newly generated OECD 416 study being secondary to maternal effects due to disturbance of microbial flora affecting food efficiency may or may not be true in an OECD 416 study were the exposure duration is long. However, it is also possible that this absence of offspring reflects a particular toxic mechanism relevant for developmental toxicity, such as perturbation in (sex) hormone balance. In this regards ECHA notes that no similar effect was noted in the OECD 421 study (Reproduction/developmental toxicity screening test) up to a dose of 1000 mg/kg using an oral gavage administration of the registered substance. As the exposure duration of an OECD 414 would be comparable to the OECD 421 such a study would further clarify whether the effects observed in the OECD 416 are indeed secondary to the poor food conversion rate or rather due to a particular toxic mechanism relevant for developmental toxicity, such as perturbation in (sex) hormone balance. In addition, as already explained above, an OECD 414 study is the standard information requirement developmental toxicity according to Annex IX, Section 8.7.2.

ECHA notes that compared to the data available when issuing the original decision, the newly provided OECD 416 study provides substantial new and relevant information that should be taken into account in performing the OECD 414 study. Firstly, the rat strain used in the OECD 416 study (Wistar rats) seems sensitive to potential developmental toxicity (whether secondary to maternal toxicity or due to a particular toxic mechanisms relevant for developmental toxicity). Secondly, oral gavage dosing used in the OECD 421 study allowed reaching higher doses without maternal toxicity than did the dietary dosing used in the OECD 416 study.

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. As detailed

above, you are required to provide a pre-natal developmental toxicity study, oral route (test method: EU B.31/OECD 414) using the registered substance subject to the present decision. The study shall be performed in Wistar rats with oral gavage dosing.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. New tests should be performed in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

This compliance check decision under Article 41 REACH, in conjunction with Article 42(1) of REACH, is necessary because in your updated registration you have provided new and relevant experimental information, which was not available to you or ECHA at the time when your registration was examined for the original decision.

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

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 did not receive any comments by the end of the commenting period.

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

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.