EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 6 August 2020

Addressee: [redacted]

Decision number: CCH-D-2114513318-54-01/F
Substance name: Triisotridecyl phosphite
EC number: 278-758-9
CAS number: 77745-66-5
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 7 November 2019

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

By decision CCH-D-2114347445-47-01/F of 16 November 2016 ("the original decision") ECHA requested you to submit information by 23 November 2018 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 following information requirement:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) rats or rabbits, oral route

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 respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[1].

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.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA
[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

Pre-natal developmental toxicity study

You were requested to submit information derived with the registered substance for Pre-natal developmental toxicity study in a first species, in rats or rabbits, oral route.

In the updated registration subject to follow-up evaluation, you have provided a pre-natal developmental toxicity (PNDT) study in rats, oral route, according to test guideline OECD 414 performed with the registered substance. The doses used in the study were 42, 125, 375 mg/kg body weight/day. You reported that there was no maternal or developmental toxicity in the study and you considered a NOAEL for maternal and developmental toxicity to be equivalent to the highest dose tested (375 mg/kg).

ECHA notes that the dose selection was based on an oral 28-day dose range finding (DFR) study of a 90-day study using doses of 0, 250, 500 and 1000 mg/kg bw/day with 5 animals per sex in the dose groups. The female animals were non-pregnant, unlike the situation in an OECD 414 study. For the DRF the report the following findings:

1. *Statistically significant increase in absolute and relative weights of liver in mid dose and high dose groups of both sexes and low dose group of male rats, in dose dependent manner. The effect was also observed in low dose group of female rats though statistical significance was not observed. Significant increases was also observed in absolute and relative weights of kidneys in all treatment groups of male rats though statistical significance was not achieved for relative weights of low dose group male rats.*
2. *Microscopic examination of liver revealed treatment related hypertrophy of hepatocytes in low and mid dose group of both sexes. These lesions were considered as effect of test item and it was supported by increase in relative and absolute weight of liver. In low dose females, hepatocellular vacuolation (4/5) was noted with minimal severity. As this lesion was not observed with similar incidence in mid dose females (1/5) and not observed in any of males animals, it could not be confirmed as related to test item treatment. Kidneys from the low- and mid- dose males and females did not reveal any alteration in microscopic examination. Livers and kidneys from the high dose animals were not examined microscopically in this dose range study.*
3. *For clinical signs of toxicity, mortality and body weight and body weight changes you report: no effects observed.*

As regards dose selection, EU Test Method B.31, OECD TG 414 states "*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".*

The duration of your DRF was 28 days. As regards female animals, which are the subject of an OECD 414 study, ECHA notes that while effects on liver weight and hepatocellular hypertrophy were noted, these did not result in clinical signs of toxicity, effects on body weight or body weight gain or mortality up to a dose of 1000 mg/kg bw/day. The exposure duration of an OECD 414 study is shorter, about 13 days. Consequently, it can neither be assumed that in an OECD 414 study, maternal toxicity (clinical signs or a decrease in body weight) would be seen using a top dose of 375 mg/kg bw/day, nor that a dose higher than 375 mg/kg bw/day would cause mortality or severe suffering.

In your comments, submitted on behalf of the registrants, you strongly disagree with ECHA's rationale for requiring additional testing. You explain that the highest dose tested in the main OECD TG 414 study (375 mg/kg bw/day) was chosen "*as it was the highest dose that would not cause mortality or severe suffering but would be assumed to induce toxicity*." You further

strengthen your justification by stating that "*significant organ weight increases were observed in the 28-day dose range study at 250 mg/kg/day*" and "*the highest dose (375 mg/kg/day) was considered a LOAEL in the companion 90-day repeated dose toxicity study*". You also consider that "*The level of maternal toxicity expected/desired in an OECD TG 414 study is not precisely dictated*", and refer to literature which according to you demonstrates that scientific experts agree that there is no precise means of dose selection for a PNDT study.

ECHA notes that the 28-day DRF study reports a LOEL of 250 mg/kg bw/day based on increased liver weights and liver hypertrophy (females). You have not provided details on the magnitude or severity of the changes in weight and histopathology. The study report considers these effects to be test-item related however no adverse effects, i.e. toxicity, were reported in the DRF study up to 1000 mg/kg bw/day. ECHA further notes that in the 90-day study, NOAEL for females was set to 375 mg/kg bw/day as the effects seen in the liver were considered to be non-adverse adaptive changes ('*No adverse effects observed at the highest dose tested*'). The LOAEL of 375 mg/kg bw/day, i.e. NOAEL of 125 mg/kg bw/day, is referring to males and the effects in testes/epididymides. ECHA notes that effects in testes/epididymides are not relevant for dose-level selection for pregnant females.

The OECD TG 414 defines the dose level setting in paragraph 14 as follows: "*At least three dose levels and a concurrent control should be used. [...] The dose levels should be spaced to produce a gradation of toxic effects. Unless limited by the physical/chemical nature or biological properties of the test chemical, 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. At least one intermediate dose level should produce minimal observable toxic effects. The lowest dose level should not produce any evidence of either maternal or developmental toxicity. A descending sequence of dose levels should be selected with a view to demonstrating any dosage-related response and no-observed-adverse-effect level (NOAEL) or doses near the limit of detection that would allow the determination of a benchmark dose. Two- to four-fold intervals are frequently optimal for setting the descending dose levels, and the addition of a fourth test group is often preferable to using very large intervals (e.g. more than a factor of 10) between dosages.*"

In light of the above, ECHA considers that the aim is to induce some developmental and/or maternal toxicity at the high dose, "*minimal observable toxic effects*" at the mid dose and then the lowest dose to derive the NOAEL, i.e. to demonstrate any possible dosage-related response.

In the main study you reported that the mean body weight, body weight change, and 20th day corrected body weight of the pregnant female rats were comparable between the control and the test item treated groups except a transitional effects on mean body weight gain during gestation period 8-11 which were not dose-dependent. There was no treatment related effect on terminal body weight. You also reported a transient effect on food consumption during the same period, which was also not dose-dependent. You reported that no clinical signs of toxicity were observed during the experimental period in any dose group and that there was no mortality. You reported no developmental toxicity during the study. You established a NOAEL at the highest dose tested (375 mg/kg bw/day) for both maternal and developmental toxicity.

In your comments you emphasise that treatment-related maternal effects were observed in the provided PNDT study, including "*statistically significant decreases in food consumption and body weight gain during portions of the gestation, and a slightly lower overall body weight gain (not statistically significant) in the high dose (375 mg/kg/day) group.*" You conclude that the study "*did induce some maternal effects while not causing death or severe suffering – in full accordance with the B.31 OECD TG 414 Guideline.*"

ECHA notes that at the high dose, the food consumption was decreased by 8.5% and body weight gain by 15.7% during gestation days 8-11. These effects were transient, and the terminal body weight was 1.9% lower in the high dose animals compared to controls. The study report concludes that "*No maternal toxicity was observed in the treated groups.*"

ECHA considers that the maternal effects (transient effects on food consumption and body weight gain on gestation days 8-11) observed at 375 mg/kg bw/day do not demonstrate that the dose would be "*the highest dose that would not cause mortality or severe suffering but would be assumed to induce toxicity*" for the purpose to induce toxicity at the highest dose as required in the OECD TG 414.

From the above findings ECHA concludes that the doses on the main OECD 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, i.e. "*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 your comments you further state that "*By seeking to reject a valid study and dictate how doses should be set only after a valid study has been conducted, ECHA fails to respect the remit of its powers, and the EU requirements particularly on vertebrate animal testing.*"

ECHA notes that a PNDT study in one species is a standard information requirement under Annex IX to REACH. In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414. ECHA further notes that the original decision requested you to provide a study according to the OECD TG 414. As explained above, ECHA considers that the doses on the main OECD TG 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, and therefore the provided study is not valid.

Finally, in your comments you estimate the exposure to be very low, and consider that additional animal testing at higher oral doses will provide no benefit to the risk assessment and risk management of this chemical. You have submitted a testing proposal to follow up the testicular findings from the 90-day study, and you consider that those results will likely determine the direction of classification and risk management of this chemical.

ECHA notes that the requested study aims at hazard assessment and identification. Exposure considerations and risk management measures can be assessed after the potential hazards have been investigated and therefore exposure considerations are not relevant in the context of this decision. Furthermore, hazard classification for reproductive toxicity, including developmental toxicity, is not dependent on dose levels in which effects are observed, and therefore testing at higher doses will provide relevant information on whether the findings would meet classification criteria for developmental toxicity. ECHA also notes that other studies, such as a follow-up to the testicular findings, will not provide information on prenatal developmental toxicity which would be equivalent to a study according to OECD TG 414. Therefore, these other studies cannot replace the requirement of a prenatal developmental toxicity study according to OECD TG 414.

As detailed above, the request in the original decision was not met, and you are still required to provide a pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance subject to the present decision and conforming to the dose selection principles of test guideline OECD 414.

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114347445-47-01/F. The 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.

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 of this decision was notified to the Member States Competent Authorities according to Article 51(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 took into account your comments and did not amend the request.

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 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.