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Helsinki, 9 September 2021

Addressee: [redacted]

Decision number: CCH-D-2114565921-43-01/F
Substance name: cis-2-tert-butylcyclohexyl acetate
EC number: 243-718-1
CAS number: 20298-69-5
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 30 August 2018

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

By decision CCH-D-2114337628-41-01/F of 18 July 2016 ("the original decision") ECHA requested you to submit information by 25 July 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) in a first species (rat or rabbit), oral route with the registered substance

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

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)[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 (Annex IX, Section 8.7.2.) in a first species

You were requested to submit information derived with the registered substance for a Pre-natal developmental toxicity study.

You have provided information on a pre-natal developmental toxicity study performed with the registered substance, via an oral route in rats.

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

1. Selection of the highest dose level in the study

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include that *"13. …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..."* and paragraph 15, *"…Dose levels should be selected taking into account any existing toxicity data as well as additional information on metabolism and toxicokinetics of the test chemical or related materials. This information will also assist in demonstrating the adequacy of the dosing regimen."*

ECHA's Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7.6.2.2.2, version 6.0, July 2017) explains further that "*The prenatal developmental toxicity study (EU Test Method B.31, OECD TG 414) provides a focused evaluation of potential effects following prenatal exposure, although only effects that are manifested before birth can be detected. More specifically, this study is designed to provide information on substance-induced effects on growth and survival of the foetuses, and increased incidences in external, skeletal and soft tissue malformations and variations in foetuses*."

Furthermore, ECHA notes in response to your comments to the draft decision that according to 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; and to derive levels of exposure to the substance above which humans should not be exposed".* Annex I, section 3.7.2.4.3, Regulation (EC) No 1272/2008, discuss practises for developmental toxicity classification, which can be used to help in dose level setting. Based on that provision it is clear that the dose level setting must be based on toxicity (or the limit dose) for classification purposes because otherwise the need for classification cannot be assessed.

In the provided study:

- The doses used in the pre-natal developmental toxicity study were 800, 2500, 7700 mg/kg feed (calculated as 55, 166 and 444 mg/kg bw/day).
- You described that the doses were selected based on results of a 14-day dose range finding study (DRF) for a previously performed 70-90-days extended OECD TG 422 study and based on the OECD TG 422 as well. The highest dose of the DRF, 15400 mg/kg diet (nominal 1000 mg/kg bw), showed a decrease in food consumption (males: -17%; females: -15%), body weight (males: not affected; females: -6%) and body weight gain (males: -25%; females: -25%), which were considered to be related to the palatability of the test material. You also stated that the test material is a fragrance

which can smell awkwardly and is therefore not tasty either. The same treated group showed a relative liver weight increase >=17%. Based on the results of the 14-day DRF, the OECD TG 422 study was performed at the highest dose of 7500 mg/kg diet (nominal 500 mg/kg bw) which showed a decrease in body weight gain (-15%) and an increase in relative liver weights in males (+14%). None of the observations was considered as adverse, therefore, the NOAEL was established at 7500 mg/kg diet, highest dose tested.

- In the pre-natal developmental toxicity study, for maternal effects observed, you reported only decreased body weight gain due to the lower food intake. More specifically, ECHA observes that according to the Tables 02 and 07 of the study report, at 7700 mg/kg, the body weight was decreased by 7% at the end of the treatment period (306.82 g in the high dose compared to 331.63 g in the control group, or 234.843 g compared to 251.722 for the body weight corrected for the gravid uterine weight). In addition, the body weight gain was decreased by 20% at the end of the treatment period (99.23 g in the high dose compared to 122.89 g in the control group).
- For maternal developmental toxicity, you reported no statistical significant differences between control and dose groups.
- For developmental toxicity, you reported a 6% decrease in foetal weight and considered it related to the lower maternal weight, for which you reported that it was 20% lower compared to the control. No effects on ossification were observed according to you. However, you reported skeletal variations related to the partly incomplete ossification.
- You established the NOAEL for maternal and developmental toxicity at >444 mg/kg bw/day (corresponding to > 7700 mg/kg in diet; highest dose tested) based on effects observed on maternal animals, i.e. decreased food intake and body weight in the high dose group, which both result from reduced palatability of the high-dose diet and thus not considered as adverse; and reduced foetal body weights, linked to the decrease in maternal food intake and body weight, which were considered as non-adverse as well.
- In your comments to the draft decision you state that you consider the dose of 500 mg/kg bw/day in the developmental toxicity study (OECD TG 414) high enough in view of the effects seen, namely a body weight decrease of -7.5% which is statistically significant, and a body weight gain reduction close to 20%. Based on that you anticipate that the effects would be more severe at higher dosages up to 1000 mg/kg bw/day, and that this would mean that the dose of 500 mg/kg bw is a justified dose.
- Because it is difficult to judge whether the effects are due to palatability or to toxicological features you acknowledge that the NOAEL of 7500 ppm (444 mg/kg bw/day) would have been applicable for maternal effects instead of the current conclusion *"no hazard identified"*, and you state that the dossier will be updated to reflect this.
- Furthermore, you propose that in case ECHA still identifies that there would be a need for additional testing to confirm that the current maximum dose of 500 mg/kg was selected appropriately, you would first perform a limited dose study, via gavage, with doses of 500 and 1000 mg/kg. If the dose at 1000 mg/kg would show sufficient toxicological effects, you would conclude that no further testing would have to be performed. The dose of 500 mg/kg bw/day by gavage would be included for comparison reasons against the existing dietary study to further confirm that it was completed correctly.

ECHA observes that in females in the extended OECD TG 422 study, the same dose levels as those in the OECD TG 414 study did not induce significant toxicity despite the longer exposure duration.

ECHA considers that your expectation that the same dose levels as used in the reproduction/developmental toxicity screening study (OECD TG 422) would be sufficiently high for the pre-natal developmental toxicity study is not plausible, due to the substantially shorter

exposure period in the pre-natal developmental toxicity study. In ECHA's view, your expectation cannot be justified, because there were no signs of developmental and/or maternal toxicity that would be relevant for the pre-natal developmental toxicity study (i.e. clinical signs or a decrease in body weights in high and medium dose) observed in the screening study (OECD TG 422). ECHA does not consider liver effects observed in male rats in the OECD TG 422 study relevant for a dose selection for the OECD TG 414 for pregnant females. ECHA is of the opinion that the design of the study provided by you does not enable the focused evaluation of potential effects on developing organism following pre-natal exposure.

Regarding the lower foetal weight in the OECD TG 414 study you already considered that it is related to the decrease in maternal body weight. As explained above, you consider as minor the 6% decrease in foetal weight whereas mean maternal body weight in the high dose group was approximately 20% lower as compared to the control group. ECHA could not identify in the results that the body weight was decreased by 20%, and considers that you have meant lower body weight gain.

Anyhow, ECHA considers that the lower corrected maternal body weight is resulting from the palatability of the test material and not a sign of the toxicity. Therefore, the lower foetal weight will be also linked to the palatability and not to the toxicity of the test material (as further discussed in Section 2 below).

In resonse to your comments ECHA re-iterates that the justification you provide for selecting the top dose (of 500 mg/kg bw/day) is not compliant with the requirements of the REACH Regulation, nor with OECD TG 414. OECD TG 414 clearly specifies that the aim should be to induce some toxicity at the top dose and minor effects at the mid dose to characterise the dose-relationship of toxic responses. Furthermore, under REACH, studies must be applicable for both classification and risk assessment. Data is adequate for classification only if toxicity is observed at the top dose or that the limit dose has been reached. The findings in your OECD TG 414 study (6% decrease in foetal weight, 20% lower body weight gain in dams) at the highest tested dose are not considered to be severe enough to exclude testing at higher doses. You also derived NOAELs at this exposure level.

Regarding your proposal to conduct "*a limited dose study via gavage, with doses of 500 and 1000 mg/kg bw/day*", ECHA understands that you mean a dose-range finding(DRF)-like study as you also mention that "*no further main study would be performed*". However, a DRF-like study with two dose levels, 500 and 1000 mg/kg bw/day, would not be sufficient as in a DRF-like study the statistical power is not high enough to conclude on the properties, and all parameters may not be investigated. Therefore, it is not sufficient for comparing the effects between dietary and gavage administrations, nor to conclude on properties for classification purposes.

It is however likely that you need a DRF study in order to decide on the appropriate dose levels for the new main OECD TG 414 via gavage. A new main study is needed with dose level setting according to OECD TG 414 and applicable for classification.

ECHA concludes that the highest dose level in the OECD TG 414 study did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity. Therefore, the prenatal developmental toxicity study provided by you is not adequate to fulfil information requirement due to the too low dose range selection in which it deviated from the test guideline OECD TG 414 and Annex I Section 1.0.1. of REACH.

Therefore, ECHA considers that the doses used in the pre-natal developmental toxicity study were not selected in accordance with the principles of the EU Test Method B.31, OECD TG 414 and ECHA Guidance on Information Requirements and Chemical Safety Assessment.

2. Selection of the route of administration

OECD TG 414 further specifies that *"17. The test substance or vehicle is usually administered orally by intubation. If another route of administration is used, the tester should provide justification and reasoning for its selection, and appropriate modifications may be necessary (3)(4)(5)..."*

You have provided a pre-natal developmental toxicity study in rats performed via oral route, administrated by feed instead of intubation. Neither a justification nor a reasoning for deviating from the recommended route of exposure has been provided.

In the high dose group, you reported lower food consumption on gestation days 0-2 (-70% average), 2-6 (-16% average), 9-12 (-18% average), 14-15 (-14.5%) and 16-21 (-17% average). In the mid dose group mean food consumption was decreased only on gestation days 0-1 (-26.6%). The study report concludes that "*The test substance is a fragrance and probably reduced palatability of the high-dose diet resulted in a lower food intake… and are not considered to be adverse*."

Furthermore, as described in the study report, the doses were selected based on a dose range finding (DRF) study performed for selecting the doses of a OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test). The DRF study also reported a decrease in food consumption (at 500 mg/kg body weight/day; males: -17%; females: -13%; and at 1000 mg/kg body weight/day; males: -17%; females: -15%) which were attributed to *"…the palatability of Verdox being a fragrance which may smell awkwardly for rats and therefore not tasty…".* Based on the results of the DRF study, a top dose of 7500 mg Verdox/kg diet (corresponding with a nominal concentration of 500 mg/kg bw) was selected.

ECHA observes that you have not justified why dosing via intubation, the default route of administration according to OECD TG 414, was not considered as an option knowing the palatability issues of the registered substance, which were already observed in the above mentioned DRF study.

ECHA considers that the lower feed consumption during a sensitive developmental window could lead to decrease in exposure to the registered substance and to limited ingestion of the registered substance in this study. Even if you apply a NOAEL of 7500 ppm the issue with the lower feed consumption remain together with the fact that exposure via the dietary route may not be high enough to comply with the requirements listed under item 1 above of the OECD TG 414 guideline and Annex I Section 1.0.1. of REACH.

Therefore ECHA concludes, in absence of a proper justification, that the study was not performed with the right route of administration, i.e. via intubation (gavage).

3. Conclusions

Based on all the above, ECHA concludes that the pre-natal developmental toxicity study provided by you is not adequate to fulfil the information requirement due to the incorrect dose setting and due to inappropriate design leading to palatability issues.

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The information requirement addressed by the original decision has not been met and you still have to provide information on an adequate pre-natal developmental study in rats, oral route (with the registered substance according to the test guideline EU B.31/OECD 414), as requested by the ECHA decision.

Additionally, ECHA recommends gavage administration as there is an indication that the animals might have issues with palatability of the registered substance.

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-2114337628-41-01/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(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 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.