ECHA
EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 28 April 2021

Addressee: [redacted]

Decision number: TPE-D-2114551547-43-01/F
Substance name: 1,3-diphenylpropane-1,3-dione
EC number: 204-398-9
CAS number: 120-46-7
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 9 July 2018

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

By decision TPE-D-2114319627-45-01/F of 19 February 2016 ("the original decision") ECHA requested you to submit information by 26 February 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(s):

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EUB.31/OECD 414) in rats or rabbits, oral route. Click here to select a HH endpoint

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

1. 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 in rats.

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

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. More specifically, according to OECD TG 414, paragraph 14, *"...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."*

Furthermore, 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".*

In the provided study:

- The doses used in the study were 100, 250, 400 mg/kg bw/day.
- You have provided the full study report. There, it is described that the doses were selected based on a dose range finding (DRF) study. In addition, it is mentioned that *"the high dose was a tolerable dose with this formulation and was not expected to cause marked toxicity."* However, you have not provided any results from the DRF study.
- In the high dose group, you reported for maternal toxicity_lower body weight (-5.5%), lower body weight gain (-14%), lower body weight change (-17%) and lower gravid uterus weight (-11%). None of the effects were considered adverse by you.
- For maternal developmental toxicity, you reported one dam of the high dose which suffered total litter loss, and increased preimplantation loss in the high dose group (9.56% vs 5.09% in control). Also, you reported slightly increased resorption rate (1.3% vs 0.6%) and post-implantation loss (9.75% vs 4.46%) in the high dose group. None of the effects were considered adverse by you.
- For developmental toxicity, you reported that there were only non-treatment related external malformations and no visceral malformations. Additionally, you reported no pattern of changes concerning ossification and therefore all variations were considered incidental or within the developmental biological spectrum. Amongst other, you reported following variations in the sternebrae in control, low, medium and high dose.
- You established the NOAEL for developmental toxicity at 400 mg/kg bw/day. You did not establish a NOAEL for maternal toxicity.

In your comments you state that based on the results of the dose range-finding (DRF) study which was attached to your comments, the testing laboratory expected the pregnant rats to tolerate 500 mg/kg bw/day of the test material. As you consider the objective of the OECD 414

study to find the No Observable Adverse Effect Level (NOAEL) for a test substance you found it appropriate to select a lower level than the levels where test substance-related toxicity was observed. In the DRF study for for repeated dose toxicity it was indicated that male rats were expected to tolerate a level of 250 mg/kg bw/day (based on weight loss > 10 % at 500 mg/kg bw/day), while female rats were expected to tolerate a level of 500 mg/kg bw/day.

You explained in your comments that to be more conservative, you reduced slightly the highest dose for the definitive OECD TG 414 study to 400 mg/kg bw/day. You mention that the testing laboratory confirmed that the reduced dose would not go against the OECD 414 guideline.

You also give the following justification for the selection of doses for the DRF study for the OECD TG 414 in your comments:

"*The dose levels of 0 (vehicle control), 100, 250 and 500 mg/kg/day of Dibenzoyl Methane were selected by the Sponsor in consultation with the Study Director. The high dose is the maximum tolerable dose with this formulation in a previous range-finding/toxicity study, and is not expected to cause marked toxicity. The low and intermediate dose levels were selected to derive a dose-response for any effects observed.*"

Dose selection for the dose-rangefinding study for the OECD TG 414 study
ECHA notes that the selection of the top dose level, 500 mg/kg bw/day, for the DRF for the OECD TG 414 was based on the DRF study for repeated dose toxicity (14-d study), where all the animals died at 1000 mg/kg bw/day. The dose of 500 mg/kg bw/day was not expected to cause marked toxicity, and indeed, in the DRF study for the OECD TG 414 study it was concluded that the pregnant rats tolerated 500 mg/kg bw/day.

However, the results from the DRF for repeated dose toxicity demonstrate that higher doses than 500 mg/kg bw/day could have been used in the DRF for the OECD 414 study, although not up to 1000 mg/kg bw/day which was lethal in the DRF for repeated toxiicty.

Dose selection for the OECD TG 414 study
The findings in the DRF study for OECD TG 414 demonstrate that dams reacted to the start of dosing by reducing food consumption, which caused slight reduction in maternal body weights. Otherwise, the dose level of 500 mg/kg bw/day was well tolerated, with only minor clinical signs (hypersalivation, alopecia, desquamation, eschar) in one or two animals (out of 5). Litter weight was slightly lower at 500 mg/kg bw/day but no other effects were reported, e.g. no effect on postimplantation loss. The lower litter weight hints to developmental toxicity which may be more pronounced at higher dose levels.

ECHA observes that in the OECD TG 414 study, the highest dose tested, 400 mg/kg bw/day, did induce neither significant maternal toxicity nor developmental toxicity. All reported findings were considered as non-adverse by you and, consequently, the NOAEL for developmental toxicity was established at 400 mg/kg bw/day, the high dose group. In addition, the intermediate dose, 250 mg/kg bw/day, did not produce any observable toxic effect.

Based on the results from this DRF study the top dose for the OECD TG 414 could have been selected to be higher than 500 mg/kg bw/day because the observed effects at the top dose were only slight, and no effects were observed at mid dose were minor effects should be detected in order to see gradual dose-responses according to the test guideline.

Purpose of the OECD TG 414 study

Based on your comments ECHA understands that you find that the objective of a definitive study (in this case a study according to OECD TG 414) is to derive a NOAEL for a test substance.

However, the justification you provide for selecting the top dose (of 400 mg/kg bw/day), despite being confirmed with the testing laboratory, is not compliant with the requirements of the REACH Regulation, nor with OECD TG 414. OECD TG 414 clearly specifies that the aim of the dose selection 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 Annex I, Section 1.0.1. of 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.

Conclusion
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.

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 (Annex IX, Section 8.7.2.; test method: EUB.31/OECD 414) in rats or rabbits, oral route.

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 TPE-D-2114319627-45-01/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 40 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.