EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 6 August 2020

Addressee: [redacted]

Decision number: CCH-D-2114509905-45-01/F
Substance name: Hexahydro-4-methylphthalic anhydride
EC number: 243-072-0
CAS number: 19438-60-9
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 27 February2019

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

By decision CCH-D-2114289309-36-01/F of 28 November 2014 ("the original decision") ECHA requested you to submit information by 28 October 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: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route

You are therefore still required to provide the 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) 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 (Annex IX, Section 8.7.2.)

You were requested to submit information derived with the registered substance for the Pre-natal developmental toxicity endpoint according to test method: EU B.31/OECD TG 414 in first species (rat or rabbit) via oral route.

In the updated registration subject to follow-up evaluation, you have provided the results of a GLP-compliant pre-natal developmental toxicity study according to OECD test guideline (TG) 414, via oral route, in rats, performed with the registered substance (the OECD TG 414 study). The doses used in the study were 0, 80, 240 and 460 mg/kg bw/day. You indicated that the doses were selected based on a dose range finding study (DRF study). In the DRF study 7 sperm positive females per dose group (0, 100, 300 and 1000 mg/kg bw/day) were treated from gestation day 5 to 19. After deaths of two dams in the high dose group, the 1000 mg/kg bw/day dose was reduced to 460 mg/kg bw/day somewhere around gestation day 8 for the remaining 5 animals. In the DRF study 3, 5, 3, 6 dams (control, low, mid and high dose group, respectively) had implantations. For evaluation of developmental toxicity there were only 3, 5, 2, 2 dams with live foetuses, respectively. One high dose dam had 100% post-implantation loss. No developmental toxicity was reported in the DRF study. Based on the results it is unclear whether or not clinical signs were noted on surviving animals with live foetuses. Furthermore, because of the low number of animals, maternal toxicity effects on body weight cannot be evaluated based on the terminal body weights (274, 297, 253 and 320 g at increasing dose levels, respectively) or corrected body weights (235, 242, 207 and 268 g at increasing dose levels, respectively). Based on the data provided no difference are however noted in corrected body weight or gravid uterus weights between the dose groups. No effects were noted in litter size or viable foetuses.

Furthermore, the dose level of 1000 mg/kg bw/day was reduced around gestation day 8 to 460 mg/kg bw/day, i.e. at the time of the implantation and immediately after that. Therefore, the intrauterine development was investigated using dose level of 460 mg/kg bw/day and not with 1000 mg/kg bw/day. ECHA notes that the total implantation loss recorded in one high dose group dam, is likely to be caused by the exposure to 1000 mg/kg bw/day, as it appears to be recorded as early embryonic death.

As explained above, based on the DRF study results there were no clinical signs or body weight changes indicating maternal toxicity and no effects indicating developmental toxicity after dosing with 460 mg/kg bw/day. While it is clear that the limit dose of 1000 mg/kg bw/day was too high and caused mortality.

In the OECD TG 414 study, you reported that no test item related changes were observed in any of the parameters investigated (maternal toxicity or developmental toxicity) in any of the doses tested.

According to both the EU Test Method B.31 and OECD TG 414 *"Unless limited by the physical/chemical nature or biological properties of the test substance, 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".*

As explained above, the DRF study did show neither developmental toxicity nor clinical signs or body weight changes indicating maternal toxicity after dosing with 460 mg/kg. Furthermore, no maternal toxicity or developmental toxicity was seen at 460 mg/kg bw/day in the main study. ECHA thus considers that the highest dose used in your pre-natal developmental toxicity study was not chosen in accordance with the aforementioned provisions set out in the EU Test Method B.31 and OECD TG 414.

Consequently, ECHA is of the opinion that the doses used in the study are not justified.
ECHA therefore concludes that the pre-natal developmental toxicity study provided by you is not adequate to fulfil the information requirement due to the too low dose range selection in which it also deviated from the test guideline.

In your comments to the draft decision you reiterate that the doses were selected in accordance with the EU method B.31/OECD TG 414 and based on the DRF study. For the DRF study results you have calculated an average dose of 640 mg/kg bw/day or 532 mg/kg bw/day depending when the initial dosing of 1000 mg/kg bw/day that was lowered to 460 mg/kg bw/day. You also commented that one animal in the 300 mg/kg bw/day group showed clinical signs (reduced activity and piloerection) in the DRF study. In addition to the clinical signs, you mention that this animal and a second animal from the same dose group showed body weight loss over the gestational days 8 to 11 and reduced food consumption.

ECHA notes, that in the DRF study at the high dose group, i.e. where the initial dose of 1000 mg/kg bw/day was administered for two days and then lowered to 460 mg/kg bw/day, the exposed animals did not show any developmental and/or maternal toxicity nor clinical signs. Concerning the clinical signs noted in one animal of the 300 mg/kg bw/day group showing reduced activity and piloerection, you state in the DRF study that the clinical signs were "*neither proved nor excluded to be due to toxicity*". Concerning the second animal in the 300 mg/kg bw/day group and the observations regarding body weight and food consumption, you state in the DRF study that no treatment related differences were noted in neither of the parameters. You also conclude that the NOAEL of the DRF study was 300 mg/kg bw/day. ECHA agrees with the statements in your dossier that no treatment related effects (neither developmental and/or maternal toxicity nor clinical signs) were noted in the two pregnant animals in the 300 mg/kg bw/day group. Therefore, based on the data provided in the DRF study it cannot be concluded that 460 mg/kg bw/day would induce some developmental and/or maternal toxicity as required for setting the highest dose in an OECD TG 414 study. This rather shows that a new DRF study going higher than 460 mg/kg bw/day is needed.

In your comments you further refer to discussions held in the MSC-RAC joint meeting held in October 2018 where it was agreed that an optimum high dose should be at or around the level were clear signs of toxicity are observed while avoiding unnecessary animal suffering. ECHA agrees on this statement. However, as described above, the animals neither in the DRF study nor in the OECD TG 414 study provided by you showed any signs of developmental and/or maternal toxicity at the selected high dose level, as required by the guideline for setting the high dose level.

Additionally, you make reference in your comments to Article 13 of TFEU, Articles 13, 25 and 47 of REACH and the OECD Guidance Document (ENV/JM/MONO(2000)7). You state that a list of severe signs and conditions that are indicators that the wellbeing of an experimental animal may be compromised is described in the OECD Guidance Document as a guide to alert staff to signs that require discussion and/or action with the aim of limiting pain and distress to an absolute minimum. You claim that the list include those signs seen in the DRF study (as described above) and which – in your view - have been taken into consideration when determining suitable dose levels for use in the main study.

ECHA notes that in the above mentioned OECD Guidance Document (ENV/JM/MONO(2000)7) lists clinical signs and conditions indicating the need for closer observation or humane killing in that particular ongoing study. However, in the DRF study non-dose dependent clinical signs (in one animal) or reduced body weights (in both animals) were noted in the mid dose group which cannot be considered as severe signs or conditions which would prevent selecting a high dose level of more than 460 mg/kg bw/day. Moreover, you yourself concluded that 300 mg/kg bw/day was the NOAEL and in addition, no effects were observed in the high dose group where the initial dose of 1000 mg/kg bw/day was administered for two days and then lowered to 460 mg/kg bw/day.

Moreover, ECHA notes that the requirements concerning animal welfare and avoiding unnecessary animals testing do not imply that vertebrate studies should not follow the specifications of the test guideline. Particularly for the animal welfare reasons, it is important that the studies are performed according to the test guidelines in order to avoid unnecessary repeats of the studies.

Further, you refer in your comments to the OECD TG 414, paragraph 14 "*Two- to four-fold intervals are frequently optimal for setting the descending dose levels ...*" and because of this you consider that selecting the dose of 460 mg/kg bw/day is adequate, because it is approximately two fold lower that the clearly toxicity dose at 1000 mg/kg bw/day. ECHA notes, that the spacing between the dose levels is not the same as the criteria for setting the highest dose. The OECD TG 414, paragraph 14 states that the highest dose should be chosen with the aim to induce some developmental and /or maternal toxicity. Based on the highest dose, descending doses are selected to demonstrate dose related responses for which two- to four-fold intervals are frequently used. Therefore, your argument on selecting the high dose level of 460 mg/kg bw/day of being two fold lower than the 1000 mg/kg bw/day dose showing toxicity in the DRF is not supported by the OECD TG 414 as for selecting the high dose itself the two- to four-fold intervals rule is not applicable. It is only meant to apply for the two lower doses to be calculated from the highest dose.

You also make reference to the paragraph of the OECD TG 414 "*Although establishment of a maternal NOAEL is the goal, studies which do not establish such a level may also be acceptable*.". You further claim that when "*dose levels should be selected with a view to demonstrating any dosage-related response and no-observed-adverse-effect level (NOAEL)....*", and the "*establishment of a maternal NOAEL is the goal*" then the objectives of the study have been met. However, the aim of the study is to select doses demonstrating a dose related trend on the potential effects and NOAEL. The identification of the NOAEL is not the main objective of the study. The main aim of the study is the identification of potential hazardous properties (OECD TG 414, paragraph 3). As the dose levels used in the above OECD TG 414 study do not meet the criteria as specified in the OECD TG 414, it is not adequate for the hazard identification purposes.

As detailed above, ECHA therefore considers that the information requirement addressed by the original decision has not been met and you still have to provide results of the prenatal developmental study in rats or rabbits, oral route using the registered substance, and according to the test guideline EU Test Method B.31/OECD TG 414, as requested in the original decision.

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-2114289309-36-01/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.