Helsinki, 4 September 2019

Addressee: [redacted]

Decision number: TPE-D-2114483466-38-01/F
Substance name: Hexahydro-4-methylphthalic anhydride
EC number: 243-072-0
CAS number: 19438-60-9
Registration number: [redacted]
Submission number: [redacted]
Submission date: 27/02/2019
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohort 3 (Developmental immunotoxicity).**

You have to submit the requested information in an updated registration dossier by ***13 September 2021***. You also have to update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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, has to 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 Ofelia Bercaru, Head of Unit, Hazard Assessment

[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

The decision of ECHA is based on the examination of the testing proposals you submitted and scientific information submitted by third parties.

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)**

a) Examination of a testing proposal

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement as laid down in column 1 of Section 8.7.3., Annex X of the REACH Regulation, whereas column 2 defines when the study design needs to be expanded.

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats to be performed with the registered substance. You have provided the following justification, according to the criteria described in column 2 of Section 8.7.3 of Annex X: "- *Inclusion/exclusion of extension of Cohort 1B: To be determined from findings of studies on similar cyclic anhydrides*
- Termination time for F2: To be determined from findings of studies on similar cyclic anhydrides
- Inclusion/exclusion of developmental neurotoxicity Cohorts 2A and 2B: To be determined from findings of studies on similar cyclic anhydrides and the proposed 90-day repeat dose toxicity study
- Inclusion/exclusion of developmental immunotoxicity Cohort 3: To be determined from findings of studies on similar cyclic anhydrides and the proposed 90-day repeat dose toxicity study".

Considerations of alternatives

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

In addition in your comments to the draft decision, you emphasised that the registered substance is a known respiratory sensitiser and has to be considered to constitute an equivalent level of concern to CMR substances due to its claimed potential to cause serious irreversible health effects. You further emphasised that stringent risk management measures for workers are already in place and that there is no exposure for professionals and consumers. Consequently, you considered that the outcome of an extended one-generation reproductive toxicity study would not result in any change of the existing risk management measures.

You further indicated that more uses than originally thought might be regarded as intermediate uses under Articles 17 and 18 of the REACH Regulation which could entail a reduction in the volume of the substance below 1000 tonnes per annum. In such case the test would no longer be required under Annex X of REACH.

In addition you noted that 4-MHHPA has been included in ECHA's 9th draft recommendation for inclusion in the Authorisation list (Annex XIV). You argue that in case of inclusion of the substance in Annex XIV list and the resulting need for authorisation, the volume of substance produced/imported into the EU will drop well below 1000 t/a,. You suggest that ECHA should postpone the present information request until there is clarity upon the inclusion of the substance in Annex XIV.

In response to these general comments ECHA notes the following:

First, Column 2 of Annex X, 8.7.3, provides that the study does not need to be conducted if the substance is already known to be a genotoxic carcinogen or a germ cell mutagen and consequently, "*appropriate risk management measures are implemented*". The fact that the substance has respiratory sensitising properties gives no indication as to its reproductive toxicity and therefore cannot justify the waiving of a requirement to provide standard information on the substance's potential to cause reproductive toxicity.

Second, you updated your dossier on 27 February 2019. The tonnage band of the joint submission and tonnage declared in the updated dossier remains above 1000 tpa. Therefore, ECHA concludes that the standard information requirements at Annex X level currently apply and consequently, maintains the request to conduct an EOGRT study.

Finally, it is undesirable to postpone this information request until inclusion of the substance in Annex XIV, given that this is an uncertain event; it is speculative whether the tonnage band will indeed go below 1000 tpa if the substance is included in Annex XIV; it can take up to three years before the Commission includes a substance in Annex XIV following an ECHA recommendation.

Study design

ECHA considers that the proposed study design needs further specification to fulfil the information requirement. The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You did not specify the premating exposure duration but proposed "as per OECD TG 443". ECHA considers that ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance2.

You proposed to that dose-level setting should be based on the findings of 90-day repeat dose toxicity study. ECHA agrees with your proposal and notes that the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

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[2] ECHA Guidance *on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

If there is no relevant data to be used for dose-level setting, it is recommended that a range-finding study (or range finding studies) is performed and that its results are reported with the main study. This will support the justifications of the dose-level selections and interpretation of the results.

Species and route selection

You proposed testing by oral route in rats. ECHA agrees with your proposal.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity. You proposed that the need to include this Cohort should be "determined from findings of studies on similar cyclic anhydrides and the proposed 90-day repeat dose toxicity study".

You have provided a GLP compliant, sub-chronic 90-day study, OECD TG 408 (2018), in rats, via oral route (gavage), at doses of 0, 50, 150, 450 mg/kg bw/day in vegetable oil using the registered substance and you set up the NOAEL at 450 mg/kg bw/day. In the absence of changes in body weight, statistically significant reduction in thymus weight was noted in low dose (-19%) and high dose (-21%) males at termination of treatment, and also in the recovery group (-22%) males. Decreased white blood cell counts were noted in females (all dose groups) and males (low and mid dose groups). No increased adrenal or decreased spleen weights (spleen weights were actually increased up to 15% in male recovery group) were noted indicating stress-related thymic atrophy and hence ECHA considers that these adverse effects, i.e. reduced thymus weight and decreased white blood cell counts, could be attributed to the immunotoxic effects of the registered substance.

Furthermore, sensitising properties of the registered substance and its structural analogues are summarised in the WHO Concise International Chemical Assessment Document 75 on cyclic acid anhydrides and their human health aspects (2009[4]). You provided a copy of this publicly available report in your registration dossier, where it is stated that: "*Allergic asthma is a well documented disease of cyclic acid anhydride exposure in workers. [...] IgE-mediated sensitization has been verified in exposed workers using skin prick tests with conjugates of the cyclic acid anhydrides and human serum albumin. Bronchial hyperresponsiveness has been correlated with specific sensitization. [...] Humans exposed to fumes from trimellitic anhydride–cured epoxy resin have been reported to exhibit pulmonary disease–anaemia syndrome, a rare disease with haemorrhagic alveolitis and specific IgG antibodies. Animal studies have demonstrated similar reactions.*"

The registered substance has a harmonised classification as a skin and a respiratory sensitiser Cat 1. Due to its respiratory sensitising properties, it is considered as a substance of very high concern (SVHC) and included in the Candidate list for authorisation. ECHA notes that, according to the ECHA Guidance[3], sensitisation is considered as supportive factor for justifying inclusion of the developmental immunotoxicity cohort.

ECHA therefore considers that the criteria to include Cohort 3 are met, because existing information on the registered substance itself and on the analogue substances derived from available in vivo studies show evidence of (developmental) immunotoxicity.

In your comments to the draft decision, you argued that based on historical control data and findings described in the full study report (which was not available for ECHA's assessment before sending a draft decision), inclusion of DIT cohort is not justified. In the updated dossier, you provided a full report of the 90-Day Oral Gavage Toxicity Study with 4-MHHPA in the Rat ([redacted] 2018), including historical control data (HCD) to

substantiate your claim.

ECHA notes that albeit HCD can be used to support the findings obtained from a study, the first comparison point is the concurrent control data. ECHA does not see any indications that the control data are not appropriate. Moreover, the absolute and relative thymus weight of the control group rats are in line with the mean HCD values. Therefore, in the absence of body weight changes, the HC data does not provide further explanation why the decreased thymus weights (absolute and relative) in the high dose group males after treatment and following recovery period would not be caused by treatment.

Concerning the reduction of number of white blood cells in female animals, the main comparison point is the concurrent control values, especially with respect to parameters related to immune systems which are known to be sensitive to the handling of animals (i.e. taking blood samples, housing etc). Albeit not statistically significant, the reduction of white blood cells numbers in females were seen in all dosed groups, indicating treatment related effects of the substance. Moreover, the control values were within the HCD ranges and consequently considered as appropriate. ECHA also notes that due to a potential sex specificity, effects can only appear in one sex.

Finally, ECHA concludes that the additional information you provided does not take away the concern on potential immunotoxic effects of the substance. Therefore, the developmental immunotoxicity Cohort 3 needs to be conducted.

b) Consideration of the information received during third party consultation

ECHA received third party information during the third party consultation. For the reasons explained below the information provided is not sufficient to fulfil this information requirement.

A third party has indicated that the substances has a harmonised classification as respiratory sensitiser and consequently, occupational exposure should be minimised. Furthermore, the third party considered that given the very low potential for exposure based on the toxicological properties of the substance and its uses, testing for reproductive toxicity would appear to be not justified.

ECHA notes that it is your responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex X, Section 8.7., column 2, or Annex XI. As outlined in the Annex X, Section 8.7., column 2, an extended one generation reproductive toxicity study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*." ECHA notes that all three criteria need to be met.

ECHA observes that the third party comment addressed only the criterion concerning low exposure. However, the third party did not prove that no systemic absorption occurs via relevant routes of exposure and that the substance is of low toxicological activity. Therefore the criteria for adaptation are not met and the information requirement for the extended one generation reproductive toxicity study cannot be adapted on this basis.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision, as specified above.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B if information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information, shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA Guidance3. You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) 14 November 2017.

ECHA held a third party consultation for the testing proposals from 28 February 2018 until 16 April 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **27 February 2019**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments.

You were notified in the draft decision that ECHA does not take into account any dossier updates after 27 February 2019. You updated your registration on 27 February 2019. ECHA took into account your comments and update 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 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 imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.