ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453322-58-01/F
Substance name: 2-methylpentane-2,4-diol
EC number: 203-489-0
CAS number: 107-41-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 24/11/2017
Registered tonnage band: Over 1000 tonnes per year

DECISION ON A TESTING PROPOSAL

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

Your testing proposals are accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rabbit), via oral route with the registered substance.**
2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, via oral route with the registered substance specified as follows:**
   - **At least two 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); and**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***17 June 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, Evaluation E3

[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 information submitted by third parties.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

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

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The dossier contains a pre-natal developmental toxicity study in rats as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint. You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to OECD TG 414 by the oral route with the registered substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that 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.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rabbit as a second species. The test in the first species was carried out with rats. According to the test method OECD 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. Hence, ECHA agrees that testing should be performed with the rabbit as a second species.

You proposed testing by the oral route, via gavage. ECHA agrees that the oral route is the most appropriate route of administration since the substance to be tested is a liquid. ECHA also considers that gavage-dosing seems appropriate based on previous oral studies.

In your comments to the draft decision you agreed to perform the requested test.

Outcome

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

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

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

a) Examination of the testing proposal

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

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 methodology, with extension of cohort 1B to mate the F1 animals to produce the F2 generation, by the oral route (gavage), in rats with a 4-week premating exposure duration to be performed with the registered substance.

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.

You have not provided a detailed justification according to the criteria described in column 2 of Section 8.7.3 of Annex X, as to why you propose an extension of cohort 1B. However ECHA considers that the proposed study design is appropriate to fulfil the information, because of the adverse effects on endocrine organs and other concerns in relation with reproductive toxicity which are observed in several studies submitted in the current technical dossier and explained in details under *"Extension of Cohort 1B"* of the present decision.

Therefore, ECHA concludes that an EOGRTS according to columns 1 and 2 of Section 8.7.3., Annex X is required with your proposed study design.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed *"4 weeks (as in the OECD 421 study)"* for the premating exposure duration. ECHA agrees with your proposal. In this specific case at least 2-week premating exposure duration for P0 animals is sufficient, because the F1 animals of Cohort 1B are mated to produce the F2 generation and thus, the premating exposure duration will be 10 weeks for these animals. Consequently the fertility parameters will be covered allowing an evaluation

of the full spectrum of effects on fertility in these animals. Therefore, the requested premating exposure duration is at least two weeks.

You proposed to set the dose level *"according to the results of the OECD 421 study"* available in your technical dossier. ECHA notes that when selecting the doses you shall aim to comply with the specific requirements of test method OECD TG 443. Therefore, 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.

Species and route selection

You proposed testing in rats by the oral (gavage) route. ECHA agrees with your proposal, since the substance to be tested is a liquid. In addition, ECHA considers that gavage-dosing seems appropriate based on previous oral studies.

Extension of Cohort 1B

If the column 2 conditions of Section 8.7.3., Annex X are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

You proposed to include an extension of Cohort 1B and but did not provide any scientific justification.

ECHA agrees that the criteria to extend the Cohort 1B are met, for the following reasons:

- The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals. Indeed the registered substance is used by professional in coatings, in cleaning agent, in lubricants, in metal working fluids, used as binder and release agents, in agrochemicals, in road and construction application; and by consumer in coatings, in cleaning agent, in lubricants and in cosmetic uses.

- Furthermore, there are indications of one or more modes of action related to endocrine disruption because adverse effects in endocrine organs, effects on fertility, reproductive parameters and development of offsprings were observed in several higher-tier studies with the registered substance, available in your technical dossier. More specifically:
  (i) both the absolute and the relative adrenal weights were increased in a sub-chronic repeated dose toxicity study (OECD TG 408, [redacted] 1999, with doses at 50, 150, and 450 mg/kg bw/day, gavage): the absolute adrenal weigths were increased in males at all doses (+18%, +16% and +19% at low, mid and high dose respectively) and in females at the highest dose (+17%). The relative adrenal weights were increased in high- and mid-dose males (+20% and +15%) respectively. Dose related increases in the adrenal weight were also reported in another repeated dose toxicity study (two-week exposure, [redacted] 1997) in both sexes, reaching statistically significance at 1000 mg/ kg/ day.

  (ii) Tendency towards increase of littering time/ length of parturition was reported in two supporting reproductive toxicity studies ([redacted], 2011 and [redacted], 2014; both using a single dose of 1000 mg/kg/day).
  This was accompanied by increased mean progesterone, decreased mean prolactin serum levels and statistically significant increase in the number of pups

found dead in the treated group (15.1% vs. 4.0% in the control group; on days 1-4 post-partum (p.p.)) resulting in a statistically significant decrease in the viability index on day 4 p.p. (84.9% vs. 96.0% in control) in the study by [redacted] (2011 – total of 19-20 days exposure, from day 6 *post-coitum* to day 4 *post-partum*).
In addition, the mean number of live pups delivered/ female was below the reference control data (12.7 vs. 13.2-16.3) and the percentage of dead pups in treatment group was above the reference control data (8.8 % vs. 5.1 %) in the study by [redacted] (2014 - from day 6 *post-coitum* to day 1 *post-partum*).

(iii) Moreover and as supporting evidence, effects on implantation loss was reported in a reproduction/developmental screening test (OECD TG 421, [redacted], 2010) and in a pre-natal developmental toxicity study (OECD TG 414, [redacted] 1997) as well. In the OECD TG 421 study, a slight increase in the post-implantation loss together with a slight increase in pup mortality up to PND 5 was reported at mid-dose, along with a marked increase in pup mortality during the five days after birth (58.6% of the live born pups, 92 out of 157) and a reduced body weight gain of the surviving pups at the high dose. In the OECD TG 414 study, the mean number of *corpora lutea* in the high-dose group was slightly increased and the mean number of implantations was slightly lower than the control values, resulting in a significant increase in the percentage pre-implantation loss.

Taken together, ECHA considers that these indications are pointing towards one or more modes of action related to endocrine disruption.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and to produce the F2 generation.

In your comments to the draft decision you agreed to perform the requested test.

b) Consideration of the information received during third party consultation

ECHA received third party information during the third party consultation. The third party provided their considerations of the study design and stated that the "*basic study design (Cohorts 1A and 1B without extension) is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*". However, the third party did not provide any scientific data which would fulfil this information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance, as specified above.

Notes for your consideration

Currently, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohorts 2A and 2B and/or Cohort 3 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's *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). 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) on 24 November 2017.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **5 September 2018**, 30 calendar days after the end of the commenting period.

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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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.