~~Confidential~~

Helsinki, 12 September 2023

Addressee(s)
Registrant of JS_106185-75-5 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
31 May 2022

Registered substance subject to this decision ("the Substance")
Substance name: (2E)-2-ethyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl)but-2-en-1-ol
EC/List number: 701-122-3

Decision number: Please refer to the REACH-IT message which delivered this communication (in format TPE-D-XXXXXXXXXX-XX-XX/F)

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***19 March 2027***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit)

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by oral route, in rats, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
   - Cohort 1A (Reproductive toxicity); and
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee(s) of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report**, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

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Reasons for the decision(s) related to the information under Annex X of REACH

1. Pre-natal developmental toxicity study

1 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in two species is a standard information requirement under Annex X, Section 8.7.2.

1.1. Information provided to fulfil the information requirement

2 Your dossier contains a PNDT study in a first species.

3 You have submitted a testing proposal for a PNDT study in a second species according to the OECD TG 414 by the oral route with the Substance.

4 ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. 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.

5 ECHA agrees that a PNDT study in a second species is necessary.

1.2. Specification of the study design

6 You proposed testing in the rabbit as a second species.

7 The study in the first species was conducted in the rat. The rat or the rabbit are the preferred species under the OECD TG 414 (Guidance on IRs and CSA, Section R.7.6.2.3.2.). Therefore, the study in the second species must be conducted in the rabbit.

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

9 You proposed to select the dose levels for the PNDT study in rabbits based on the existing studies that were conducted in rats (OECD TG 408, OECD TG 422 and OECD TG 414). You indicated in your testing proposal justification that 'In these studies, the only adverse effects were observed in gestating females at 750 mg/kg bw/day in the OECD guideline 414 study in rats and at 1000 mg/kg bw/day in the OECD guideline 422 study. The NOAEL for maternal toxicity was set at 300 mg/kg bw/day. Therefore, (…) the dose level selection for the Pre-natal developmental Toxicity Study in rabbits will be based on this information, ensuring that toxicity in females is considered.'

10 ECHA notes that due to the significant inter-species differences between rat and rabbit, information gathered for the rat cannot be used to inform on dose-level selection for the rabbit. Dose-level selection for an OECD TG 414 study in rabbits should be based on existing information on the same species, i.e. from studies performed in rabbits[2].

1.3. Outcome

11 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

2. Extended one-generation reproductive toxicity study

[2] For more information and recommendations, see '*Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH*': https://echa.europa.eu/documents/10162/17220/211221_echa_advice_dose__repro_en.pdf/27159fb1-c31c-78a2-bdef-8f423f2b6568?t=1640082455275

12 The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X. Furthermore, Annex X, Section 8.7.3., Column 2 defines when the study design needs to be expanded.

2.1. Information provided to fulfil the information requirement

13 You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the Substance.

14 ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. 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.

15 ECHA received third party information concerning the testing proposal during the third-party consultation.

16 The third party provided their considerations of the proposed study design (Cohorts 1A and 1B, with the extension of Cohort 1B) and stated that 'the criterion triggering extension of this cohort do not appear to have been met. The substance does not display genotoxic effects in somatic cell mutagenicity tests in vivo which could lead to classifying it as Mutagen Category 2; there are no indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure; and there are no indications of one or more relevant modes of action related to endocrine disruption from available in vivo studies or non-animal approaches. Consequently, if the testing proposal is approved by ECHA, this should be without the extension of Cohort 1B to include the F2 generation'.

17 ECHA addresses the study design under section 2.2. below.

18 ECHA agrees that an EOGRTS is necessary.

2.2. Specification of the study design

2.2.1. Species and route selection

19 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the species preferred by OECD TG 443.

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

2.2.2. Pre-mating exposure duration

21 The length of the pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

22 You proposed two weeks pre-mating exposure duration. ECHA disagrees with your proposal.

23 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter pre-mating exposure duration (Guidance on IRs & CSA, Appendix R.7.6-3).

2.2.3. Dose-level setting

24 You proposed to select the dose levels for the EORGTS based on the existing studies that were conducted in rats (OECD TG 408, OECD TG 422 and OECD TG 414). You indicated that 'In these studies, the only adverse effects were observed in gestating females at 750

mg/kg bw/day in the OECD guideline 414 study and at 1000 mg/kg bw/day in the OECD guideline 422 study. The NOAEL for maternal toxicity was set at 300 mg/kg bw/day. Therefore, (…) the dose level selection for the EOGRTS will be based on this information, ensuring that toxicity in both female and male animals is considered.' ECHA agrees that all available and relevant information should be taken into account.

25 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

26 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Annex I, Section 3.7.2.4.4. to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

27 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

28 In summary: Unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(4) the highest dose level in P0 animals must follow the limit dose concept.

29 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

30 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

2.2.4. Cohorts 1A and 1B

31 Cohorts 1A and 1B belong to the basic study design and must be included.

2.2.4.1. Histopathological investigations in Cohorts 1A and 1B

32 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, para. 67 and 72) if

- the results from Cohort 1A are equivocal,

- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

2.2.4.2. Splenic lymphocyte subpopulation analysis

33 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, para. 66; OECD GD 151, Annex Table 1.3).

2.2.4.3. Investigations of sexual maturation

34 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, para. 12 in conjunction with OECD TG 443, para. 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

2.2.5. Extension of Cohort 1B

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

36 You proposed to include an extension of Cohort 1B.

37 The extension is required, among others, if the use of the Substance is leading to significant exposure of consumers or professionals (column 2, first para., point (a) of Section 8.7.3.) and if there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure (column 2, first para., point (b), second indent of Section 8.7.3.).

38 The use of the Substance reported in the joint submission is leading to significant exposure of consumers and/or professionals because the Substance is used by professionals e.g. in washing and cleaning agents (e.g. PROCs 10, 11, 13) and additionally by consumers in air care products, biocides as well as washing and cleaning products.

39 With regard to point (b), you note that 'as no toxicokinetic data are available to define a steady state in test animals after prolonged exposure, criterion b) could not be fully assessed. Therefore, the extension of the Cohort 1B to generate the second generation is justified as the triggers described in Column 2 have been only partially met.'

40 ECHA notes that there are no indications that the internal dose for the Substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure. Specifically, the logKow for the substance/metabolite(s) is below 4.5, and there are no effects observed at more than 3 times lower exposure levels in the 90-day study compared to effects in the 28-day study. Furthermore, ECHA notes that lack of toxicokinetic data is not an indication that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure.

41 For the reasons stated above, ECHA concludes that the conditions described in Annex X, Section 8.7.3., Column 2 are not met. Therefore, ECHA disagrees with your proposal and considers that Cohort 1B must not be extended.

2.3. Outcome

42 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with the Substance, as specified above.

2.3.1. Further expansion of the study design

43 The conditions to include the extension of Cohort 1B are currently not met. Furthermore, 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 Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 26 August 2022.

ECHA held a third-party consultation for the testing proposal(s) from 26 October 2022 until 12 December 2022. ECHA received information from third parties (see corresponding Appendix/Appendices)

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

ECHA did not receive any comments within the commenting period.

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: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[3].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

[3] https://echa.europa.eu/practical-guides

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

2. General recommendations for conducting and reporting new tests

References to Guidance on REACH and other supporting documents can be found in Appendix 1.

[4] https://echa.europa.eu/manuals