~~Confidential~~

Helsinki, 17 June 2022

Addressees
Registrants of [redacted] as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
16/04/2021

Registered substance subject to this decision ("the Substance")
Substance name: 2,2'-ethylenedioxydiethyl bis(2-ethylhexanoate)
EC number: 202-319-2

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)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***24 March 2025***.

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).

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 addressees 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.

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Appendix 1: Reasons for the decision

Contents

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. to REACH.

1.1. Information provided to fulfil the information requirement

2 You have submitted a testing proposal for a PNDT study according to OECD TG 414 with the Substance.

3 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.

4 Despite your considerations of no available alternative methods, you have provided, within IUCLID, a waiving proposal for the pre-natal developmental toxicity in a second species: "*[…] According to Annex IX Column 2, a decision on the need to perform a study at the >100 t/y level, or at the next level thus at the > 1000 t/y level, on a second species should be based on the outcome of the first test and all other relevant available data. […] From an anatomical and physiological viewpoint, there are few differences between rats and rabbits, actually molecules are readily transferred from dams to fetuses in the placenta type of rodents, rabbits and primates, whereas their uptake by other (large) species is very low (Furukawa et al., 2014). However, the rabbit is known as a difficult species, as maternal gastro-intestinal intolerance may prevent testing higher dose levels. […] Based on toxicokinetics assessment of the test item, oral absorption is assumed to be limited. A waiver for a second species is proposed based on expected gastro-intestinal intolerance in rabbits, which may prevent to test higher dosages and volumes. A second species teratogenicity study is not expected to lead to better assessment of developmental toxicity potential*."

5 To support your adaptation, you refer to the following studies with the Substance, in rats: OECD TG 422, OECD TG 408, OECD TG 414 and OECD TG 443. You conclude that these studies did not demonstrate the need to classify the substance for reproductive or developmental effects. None of these studies resulted in a trigger for an OECD TG 414 study in a second species.

6 Furthermore, you present a consideration that a study with rabbits may not be feasible because rabbits are sensitive to gastro-intestinal disturbances which may prevent to test high dosages and it is not expected to lead to better assessment of developmental potential.

1.2. Assessment of the information provided

7 We have assessed this information and identified the following issues:

1.2.1. Wrong Column 2 adaptation

8 You refer correctly to Annex X Column 1 information requirements but also in addition to Annex IX Column 2, where study in second species is triggered based on the outcome of the first test and all other relevant available data.

9 ECHA notes that the pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X and not subject to any conditions.

1.2.2. Unsuitability of the rabbit as a second species

10 According to OECD TG 414, the preferred rodent species is the rat, and the preferred non-rodent species is the rabbit. Justification should be provided if another species is used.

11 You consider that the test in a second species, rabbit, may not be feasible. You argue that the rabbit is known as a difficult species, as maternal gastro-intestinal intolerance may prevent testing higher dose levels and based on toxicokinetics assessment of the test item, oral absorption is assumed to be limited.

12 ECHA notes that you have not provided any experimental information in rabbits that would allow ECHA to verify whether, for example the rabbit would be more sensitive than the rat to exposure of the Substance, or that the oral absorption of the Substance would be limited in the rabbit.

13 In any case, Guidance on IRs and CSA, Section R.7.6.2.3.2, states that "*The selection of the species for the prenatal developmental toxicity study should be made taking into account substance-specific aspects*", and that "*If a species other than the rat and the rabbit is selected as the first or second species, the selection should be justified*".

14 In conclusion, the postulated rabbit-specific toxicity cannot – even if demonstrated – be considered as a justification to waive the standard information requirement of a pre-natal developmental toxicity study in a second species. It can only justify the use of another species, other than the rabbit, for the study. However, no justification for the use of another species has been provided.

15 For the reasons explained under sections 1.2.1. and 1.2.2. above, your adaptation is rejected. ECHA agrees with your testing proposal for a PNDT study in a second species.

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

1.3. Specification of the study design

17 You proposed testing in the rabbit as a second species. 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 (ECHA Guidance R.7a, Section R.7.6.2.3.2.). Therefore, the study must be conducted in the rabbit.

18 ECHA considers that if there were substance-specific data to show that the Substance causes gastro-intestinal disturbance in the rabbit, that the resulting toxicity is not relevant for humans and would limit the hazard assessment of the Substance for pre-natal developmental toxicity, this would indicate that the rabbit is not an appropriate non-rodent species to test the Substance and other non-rodent species should be evaluated.

19 You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is the most appropriate to investigate reproductive toxicity (ECHA Guidance R.7a, Section R.7.6.2.3.2.).

1.4. Outcome

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

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

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).

All Guidance on REACH is 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 30 April 2021.

ECHA held a third party consultation for the testing proposal(s) from 1 July 2021 until 16 August 2021. ECHA did not receive information from third parties.

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

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

ECHA took into account your comments and amended the deadline.

> In your comments on the draft decision, you requested an extension of the deadline to provide information from 18 to 30 months from the date of adoption of the decision. You supported your request with justification from the laboratory that there are substantial delays foreseen before the testing in the selected testing facility can start.
>
> On this basis, ECHA has granted the request and extended the deadline to 30 months.

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: Addressees 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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[2].

(4) 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 shall 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.

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[3].

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