~~Confidential~~

Helsinki, 3 January 2023

Addressees
Registrant(s) of JS_500-303-2 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14/09/2021

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-Isopropylidenediphenol, ethoxylated, esters with fatty acids, coco
EC number: 500-303-2

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)

Your originally proposed test using the Substance is rejected, according to Article 40(3)(d):

In vivo mammalian erythrocyte micronucleus test (EU B.12./OECD TG 474)

The reasons for the decision are explained in Appendix 1.

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

[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

Contents

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

1. In vivo mammalian erythrocyte micronucleus test

1 An appropriate *in vivo* somatic cell genotoxicity is an information requirement under Annex IX to REACH (Section 8.4., Column 2) if (1) there is a positive result in any of the in vitro genotoxicity study under Annex VII or VIII to REACH and (2) there are no results available from an *in vivo* study.

2 Your dossier contains "ambiguous" results for the *in vitro* cytogenicity test (OECD TG 487, 2018) which you claim raise the concern for chromosomal aberrations. Moreover, no data from an in vivo somatic cell genotoxicity study are available in the dossier.

1.1. Information provided to fulfil the information requirement

3 You have submitted a testing proposal for an *in vivo* mammalian erythrocyte micronucleus test to be performed with the Substance.

4 ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity in vivo. 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 received third party information concerning the testing proposal during the third-party consultation.

6 A third party has indicated that the *in vitro* data in your dossier does not appear to clearly trigger a requirement for additional testing *in vivo* since the *in vitro* gene mutation study in bacteria (OECD TG 471, 2018) is not clearly negative and the *in vitro* micronucleus test (OECD TG 487, 2018) is equivocal.

7 As already stated above, ECHA notes that the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered under Annex VIII to REACH (Section 8.4., Column 2) in case of a positive result in any of the in vitro genotoxicity studies under Annex VII or VIII to REACH.

8 To justify your testing proposal, you have provided results from:

(i) an *in vitro* gene mutation study in bacteria (OECD TG 471, 2018) that you considered negative while you still noticed a statistically significant increase of revertant colony numbers in Salmonella typhimurium TA 100 compared to the negative control.

(ii) an *in vitro* micronucleus test (OECD TG 487, 2018) that you considered as "not clearly positive" because of the doubling of the number of micronuclei at the highest test concentration compared to the negative control after a 3-hr exposure without metabolic activation, but not reaching statistical significance.

9 We have assessed the provided information and identified the following issues:

10 Regarding study (i), ECHA notes that the increase in mutant frequency in *Salmonella typhimurium* TA 100 compared to the negative control was below the 2-fold increase threshold commonly used to define a positive response in this strain. In addition, no concentration-related increase was reported. Therefore, ECHA agrees that this increase may not be biologically relevant. However, you did not provide historical control data to

compare them with the mutant frequencies obtained in this study and help in the evaluation of the test results.

11 Furthermore, since you defined your evaluation criteria based on statistical analysis (Student's t-test) and statistical significance was reached at all test concentrations in this strain, with and without metabolic activation, those results could be considered equivocal. According to OECD TG 471, equivocal results should be clarified by further testing. However, you did not perform any repeat experiment to clarify or confirm the results obtained.

12 Regarding study (ii), ECHA notes that no statistical analysis and no historical control data are reported in your dossier or in the full study report. Without this information it is not possible to properly evaluate the increase in micronuclei observed in the short-term treatment condition without metabolic activation. Therefore, ECHA agrees that this increase can be considered equivocal.

13 According to OECD TG 487, equivocal results should be clarified and further testing could be useful. However, you did not perform any repeat experiment to clarify or confirm the results obtained.

14 Overall, the provided *in vitro* studies do not clearly indicate a concern for chromosomal aberration. Therefore, ECHA considers that an *in vivo* mammalian erythrocyte micronucleus test is not justified at this tonnage band.

1.2. Outcome

15 Your testing proposal is rejected under Article 40(3)(d) of REACH.

16 In the comments to the draft decision, you agree with ECHA’s assessment of the provided information.

17 Moreover, in your comments you ask if you need to conduct an *in vitro* gene mutation study in mammalian cells.

18 We note that an *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test. Since your dossier contains negative/equivocal results for both an Ames test and an *in vitro* cytogenicity study the requirement of Annex VIII, Section 8.4.3. is triggered. Either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable. You are not required to submit a testing proposal as this test covers an endpoint of Annex VIII.

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

This decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 9 November 2020.

ECHA held a third party consultation for the testing proposal(s) from 21 January 2021 until 8 March 2021. ECHA received information from third parties (see Appendix 1, Section 1).

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.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the reasons for the decision.

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

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 and VIII to REACH, for registration at 10-100 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.