~~Confidential~~

Helsinki, 17 June 2022

Addressees
Registrant(s) of JS_DMM_210-848-5 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
13/06/2016

Registered substance subject to this decision ("the Substance")
Substance name: Dimethyl maleate
EC number: 210-848-5

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***26 June 2023***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102

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

2. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

3. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203)

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.

Appendix 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

1 An in vitro gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

1.1. Information provided

2 You have provided:

(i) In Vitro gene mutation study in bacteria (1982) with the Substance.

1.2. Assessment of the information provided

3 We have assessed this information and identified the following issue(s):

1.2.1. Study not adequate for the information requirement

4 To fulfil the information requirement, the study must meet the requirements of OECD TG 471 (2020). Therefore, the following specifications must be met:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

5 The study (i) is described as an in vitro gene mutation study in bacteria (equivalent or similar to OECD TG 471). However, the following specifications are not according to the requirements of OECD TG 471 (2020):

a) the required fifth strain (S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) was not included.

6 The information provided does not cover one of the key parameters required by OECD TG 471.

7 Therefore, the information requirement is not fulfilled.

8 In your comments on the initial draft decision you agree to conduct the study.

1.3. Specification of the study design

9 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) should be performed using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

Reasons related to the information under Annex VIII of REACH

2. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

10 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

2.1. Information provided

11 You have adapted this information requirement by using Column 2 of Annex VIII, Section 8.4.2. To support the adaptation, you have provided following information:

(i) A justification: "An in vivo study on the chromosome aberration endpoint is available, that replaces the in vitro study".

(ii) In vivo mammalian erythrocyte micronucleus test with the Substance (1982).

2.2. Assessment of the information provided

12 We have assessed this information and identified the following issue(s):

2.2.1. Column 2 adaptation criteria not met

13 Under Section 8.4.2., column 2 of Annex VIII to REACH, the study usually does not need to be conducted "if adequate data from an in vivo cytogenicity test are available". The Guidance on IRs and CSA, Section R.7.7.6.3 and Table R.7.7–3 clarifies that the in vivo somatic cell cytogenicity test must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively.

14 For the data from an in vivo somatic cell cytogenicity test to be considered adequate, the in vivo study you submitted has to meet the requirements of OECD TG 474, and the specifications/conditions of this test guideline include:

a) The study must include a minimum of three doses/groups of treated animals, as well as a negative control group and a positive control group.
b) The proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood).

15 The study (ii) is described as an in vivo mammalian erythrocyte micronucleus test (equivalent or similar to OECD TG 474). However, the following specifications are not according to the requirements of OECD TG 474

a) the appropriate number of doses, as only one dose level was used.
b) data on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals.

16 The information provided does not cover specifications/conditions required by OECD TG 474. The column 2 criteria are not met.

17 Therefore, your adaptation is rejected.

18 In your comments on the initial draft decision you agree to conduct the study.

2.3. Specification of the study design

19 To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

3. In vitro gene mutation study in mammalian cells

20 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (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.

21 Your dossier contains data for an in vitro gene mutation study in bacteria, and data for an in vivo mammalian erythrocyte micronucleus study.

22 The information for the in vitro gene mutation study in bacteria and for the in vivo mammalian erythrocyte micronucleus study provided in the dossier is rejected for the reasons provided in sections 1. and 2.

23 The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro cytogenicity study in mammalian cells will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

24 You have not submitted any information for this requirement.

25 Consequently, you are required to provide information for this endpoint, if the in vitro gene mutation study in bacteria and the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provide negative results.

~~26~~ In your comments on the initial draft decision you agree to conduct the study in case of negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

3.1. Specification of the study design

27 To fulfil the information requirement for the Substance, 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.

4. Short-term toxicity testing on fish

28 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

4.1. Information provided

29 You have provided the following information:

(i) a study according to DIN 38412 Teil 15, from 1977, with the Substance

4.2. Assessment of the information provided

30 We have assessed this information and identified the following issue:

31 To fulfil the information requirement, a study must comply with OECD TG 203 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- the analytical measurement of test concentrations is conducted (validity criterion);
- the test duration is 96 hours or longer;
- the test design is reported (*e.g.* static, semi-static or flow-through, number of test animals);
- the test procedure is reported (*e.g.* composition of the test medium, fish loading);
- the test conditions are reported (*e.g.* test temperature, pH, dissolved oxygen, salinity);
- mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) are reported. The frequency of observations includes at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4.

32 Your registration dossier provides short-term fish toxicity study showing the following:

- no analytical measurement of test concentrations was conducted;
- the test duration was 48 hours;
- information on test design (test type, number of test animals, test concentrations and number of replicates used), on test procedure (composition of the test medium, fish loading) and test conditions (test temperature, pH, dissolved oxygen, salinity) is not reported;
- tabulated data on mortalities and sub-lethal effects (*e.g.* with regard to equilibrium, appearance, ventilator and swimming behaviour) obtained on at least 2 observations within the first 24 hours and at least two observations per day from day 2 to 4 for each treatment group and control are not reported.

33 Based on the above:

- the validity criterion of OECD TG 203 on analytical measurement of test concentrations is not met; and
- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically the test duration was shorter than required by OECD TG 203 and furthermore, the reporting of the study is not sufficient to conduct an independent assessment of its reliability in respect of test design, procedure, conditions and of results of effects investigated.

34 Therefore, the requirements of OECD TG 203 are not met.

35 In your comments on the initial draft decision you indicate your intention to provide a QSAR adaptation to fulfil the information requirement. The information in your comments is not sufficient for ECHA to make an assessment because you have only provided an intention to adapt without supporting information. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

36 On this basis, the information requirement is not fulfilled.

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 further compliance checks at a later stage on the registrations present.

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

The compliance check was initiated on 04 May 2021.

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

ECHA took into account your comments and did not amend the request(s).

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.

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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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- 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[2].

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