~~Confidential~~

Helsinki, 27 March 2023

Addressees
Registrant(s) of JS_106-65-0 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
16/10/2019

Registered substance subject to this decision ("the Substance")
Substance name: Dimethyl succinate
EC number: 203-419-9

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 information under request 1 below by ***2 July 2025*** and all other information listed below by ***2 December 2026***.

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

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat)

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

3. 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.

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

2 ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following sections.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Predictions for toxicological properties

5 You provide no read-across justification document.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

- DBE, Dibasic esters mixture (Dimethyl glutarate - [redacted] dimethyl succinate - [redacted] dimethyl adipate - [redacted])

7 You provide the following reasoning for the prediction of toxicological properties:

- for DBE: "*The basis for considering dimethyl succinate, dimethyl glutarate, dimethyl adipate and a dibasic ester mixture containing all three as a Category is based upon the similarities of the three substances in structure, physicochemical properties and consistent responses in ecotoxicology and human health toxicology studies*" and "*The source substance is a mixture containing the target substance, all being components of the mixture being dimethyl esters of acids which are metabolised to endogenous substances.*"

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.1.1. Missing supporting information

10 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and

establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

11 Supporting information must include bridging studies to compare properties of the Substance and source substances.

12 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

13 You provided the following supporting information:

(i) An in vivo inhalation study (TG 413, 1987), with the source substance DBE;
(ii) An in vivo inhalation study (TG 413, 1990), with the source substance DBE;
(iii) An in vivo inhalation study (eq. TG 414, 1995), with the source substance DBE;
(iv) An in vivo inhalation study (eq. TG 415, 1998), with the source substance DBE;
(v) A prediction from a (Q)SAR model, 2019.

14 Specific reasons why these studies cannot be considered reliable are explained further below under the relevant information requirement sections 1 and 2. Thus, the data set reported in the technical dossier does not include relevant, reliable and adequate information neither for the Substance, nor for the source substance(s), to support your read-across hypothesis.

15 In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

0.1.1.2. Adequacy and reliability of source studies

16 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

17 Specific reasons why the studies on the source substance(s)(i.e. studies i-v) do not meet these criteria are explained further below under the applicable information requirement sections 1 and 2. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion on the read-across approach

18 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

Reasons related to the information under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

19 A sub-chronic toxicity study (90 day) is an information requirement under Annex IX, Section 8.6.2.

1.1. Information provided

20 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances:

(i) An in vivo inhalation study (TG 413, 1987), with the source substance DBE;

(ii) An in vivo inhalation study (TG 413, 1990), with the source substance DBE;

1.2. Assessment of the information provided

1.2.1. Read-across adaptation rejected

21 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

1.2.1.1. Adequacy and reliability of studies on the source substance(s)

22 As explained in the Appendix on Reasons common to several requests, under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 408. Therefore, the following specifications must be met:

a. highest dose level should aim to induce toxicity or reach the limit dose;

b. clinical signs observed daily and functional observations week 11 or after, i.e. sensory activity, grip strength and motor activity assessments;

c. the oestrus cycle in females at necropsy.

23 Your registration dossier provides two studies (i. and ii.) according to an OECD TG 413 showing the following:

a. no justification for the dose setting while the highest dose levels tested was 1 mg/L air, which is below the limit dose of the test guideline, and no adverse systemic effects were observed.

   The highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering. In both studies the highest dose level did not reach the limit dose or induce significant systemic toxicity. Only local effects on the olfactory epithelium were observed. Both studies were conducted via inhalation route, which ECHA does not consider the most appropriate route of administration due to the low vapour pressure of the tested substance (23.5 Pa for dimethyl succinate at 25 C), and due to the local toxicity which limits the maximum dose.

b. data on clinical signs and functional observations are missing: nature, severity and duration;

c. data on oestrus cycle are missing.

24 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 408 and these studies are not an adequate basis for your read-across predictions.

25 In the comments to the draft decision, you agree to perform the requested study.

1.3. Specification of the study design

26 Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

27 According to the OECD TG 408, the rat is the preferred species.

28 Therefore, the study must be performed in rats according to the OECD TG 408 with oral administration of the Substance.

2. Pre-natal developmental toxicity study in one species

29 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

2.1. Information provided

30 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances:

(i) An in vivo inhalation study (eq. TG 414, 1995), with the source substance DBE;
(ii) An in vivo inhalation study (eq. TG 415, 1998), with the source substance DBE.

31 You have also adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) A prediction from a (Q)SAR model, 2019.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

32 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

2.2.1.1. Adequacy and reliability of studies on the source substance(s)

33 As explained in the Appendix on Reasons common to several requests, under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 414. Therefore, the following specifications must be met:

a) the highest dose level aims to induce toxicity or aims to reach the limit dose;

b) the test chemical is administered via oral gavage;
c) the dams are examined for weight and histopathology of the thyroid gland, thyroid hormone measurements.

34 Your registration dossier provides a study similar to an OECD TG 414 and similar to a OECD TG 415 showing the following:

a) the highest dose levels tested was 1 mg/L air, which is below the limit dose of the test guideline, and no adverse effect were observed;
b) the substance was administered by inhalation without justification and in the presence of dose-limiting toxicity at local site of contact;
c) data on the examination of the foetuses, including incidence and severity, are missing; In particular, the following investigations are missing: weight and histopathology of the thyroid gland, thyroid hormone measurements.

35 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the one specified in the corresponding OECD TG.

36 The studies are not adequate for the information requirement and are therefore rejected.

2.2.2. QSAR adaptation rejected

37 REACH Guidance Chapter R.6.1.3.2 specifies that the regulatory relevance of a (Q)SAR expresses the usefulness of the predicted endpoint in relation to the information needed for the regulatory purpose.

38 ECHA Practical Guide on How to use and report (Q)SARs Chapter 3.3 specifies that results from (Q)SAR models are adequate for risk assessment or classification and labelling when they are equivalent to results obtained from the required experimental test. The corresponding study that shall normally be performed for this particular information requirement is OECD TG 414, which measure(s) amongst others, NOAEL, visceral, skeletal and fetal parameters.

39 You have provided the prediction from a (Q)SAR model: consensus model prediction for developmental toxicity from the Danish QSAR database. According to the provided documentation, the training set consists of clinical, epidemiologic and animal data.

40 The prediction does not give information on species, NOAEL, visceral, skeletal and fetal parameters.

41 The prediction is qualitative and it is not known on what the conclusion of "(non) developmental toxicity" is based on. The training set considers data from different species and experimental protocols to make the overall conclusion on "developmental toxicity".

42 Therefore, the prediction is not adequate to meet the information requirement for developmental toxicity for the purpose of classification and labelling and/or risk assessment.

43 The study is not adequate for the information requirement and is therefore rejected.

2.3. In the comments to the draft decision, you agree to perform the requested study. Specification of the study design

44 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

45 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

46 Therefore, the study must be conducted in rats with oral administration of the Substance.

Reasons related to the information under Annex X of REACH

3. Pre-natal developmental toxicity study in a second species

47 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X, Section 8.7.2.

3.1. Information provided

48 You have attempted to adapt this information requirement by using Annex IX, Section 8.7.2, Column 2.

3.2. Assessment of the information provided

49 You have not provided a valid adaptation according to the general rules of Annex XI, nor the specific rules of Annex X Section 8.7.2 Column 2.

50 The legal provision of A.IX Section 8.7.2 column 2 that you refer to is not an adaptation possibility for waiving an experimental study at Annex X. Instead, it lays out the conditions under which a PNDT-study is triggered in a second species, based on (hazardous) effects observed in a PNDT with the first species; at Annex IX. Your substance is registered at Annex X, for which the submission of a PNDT study in a second species is an information requirement.

51 Therefore, your adaptation is rejected.

52 In the comments to the draft decision you disagree with the request of a pre-natal developmental toxicity study (Annex X, Section 8.7.2, test method: OECD 414) in a second species. You state that "*no gain in information is expected when testing the second species*".

53 As indicated further above, at this tonnage level (i.e. quantities of 1000 tonnes, or more, per annum), a PNDT study in a second species is the default standard information requirement.

54 In your comments you are referring to scientific literature and in particular to the scientific article Braakhuis et al. (2019) which concluded that rat and rabbit do not differ significantly in sensitivity of developmental effects. However, sensitivity considerations alone are not sufficient to establish that testing in a second species is not needed because:

a. results of pre-natal developmental toxicity studies with rats and rabbits may differ significantly with respect to the effects observed due to species differences (e.g. thalidomide), and

b. there are no concentration limits for classifying a substance for developmental toxicity (e.g. malformations observed at high-dose only can be used for hazard identification such as classification and labelling).

55 Furthermore, the article by Braakhuis et al. (2019) does not contain any Substance-specific information that would meet the information requirement for second species PNDT at Annex X.

56 You also state that "a prenatal developmental toxicity study in a second species will result in unnecessary deaths of animals". ECHA notes that animal welfare is not on its own a legal ground for adaptation under Column 2 of Annex X or under the general rules of adaptation under Annex XI.

57 Last, you refer to Annex IX, Sections 8.7 and 8.7.2, Column 2 of the REACH Regulation. Please note that for the standard information requirement of a PNDT in a second species at Annex X, the adaptation possibilities set out in Annex X, Section 8.7, Column 2 apply. In this context, under Annex X, Section 8.7. Column 2, third paragraph, a PNDT study in a second species at Annex X may be adapted where a substance is known to cause developmental toxicity, meeting the criteria for classification in the hazard class reproductive toxicity (category 1A or 1B:May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment

58 The information provided in your comments does not change the assessment.

3.3. Specification of the study design

59 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study in the first species was carried out by using a rodent species (rat).

60 Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

61 The study must be performed with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

62 Based on the above, the study must be conducted in rabbits with oral administration of the Substance.

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

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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 15 November 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 requests but amended the deadlines.

In your comments, you requested an extension of deadlines. The deadlines of the draft decision were set based on standard practice for carrying out OECD TG tests. The deadline for request 1 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.

For requests 2 and 3 you requested an extension of the deadline from 24 to 41 months. Your request was supported by documentary evidence from a testing laboratory. ECHA has extended the deadline for requests 2 and 3 to 41 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 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]
[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) 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.

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