~~Confidential~~

Helsinki, 20 September 2023

Addressee(s)
Registrant(s) of C4-C6_diisobutylester as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
27/09/2021

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of bis(2-methylpropyl) pentanedioate and bis(2-methylpropyl) butanedioate and bis(2-methylpropyl) hexanedioate
EC/List number: 907-870-9

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 7 below by ***7 January 2026*** and all other information listed below by ***4 January 2027***.

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

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

1. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020))

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

3. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei

4. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490)

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

5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

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

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

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

Information required depends on your tonnage band

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 request(s)
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 request(s)

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Reasons common to several requests

0.1. Read-across adaptation rejected

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

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

2 In addition, you have provided a weight of evidence adaptation under Annex XI, Section 1.2 for the following standard information requirement for which you have included a study on analogue substances whose reliability must be assessed under Annex XI, Section 1.5:

- *In vitro* micronucleus study (Annex VIII, Section 8.4.2.)

3 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.

4 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.

5 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. Scope of the grouping of substances (category)

6 You provide a read-across justification document in IUCLID Sections 7.5, 7.6, 7.8.

7 You justify the grouping of the substances as: "The similarities in molecular structures, properties, functions and uses of the dibasic esters enables read-across of the available data to fulfil specific information requirements under REACH".

8 You define the applicability domain as: "All category members of the dibasic esters category are the reaction product of an alcohol (methanol, butanol or isobutanol) with the single dicarboxylic acids, succinic, glutaric or adipic acids or mixtures of these acids. The ester bonds are effectively metabolised by the body releasing the component alcohols and acids. The difference between members involves 3 parameters: 1) the alcohol used to esterify the acids, 2) the length of the acid molecule (4C, 5C or 6C) and 3) the presence of individual esters or mixtures thereof".

9 ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

0.1.2. Predictions for toxicological properties

10 You provide a read-across justification document in IUCLID Sections 7.5, 7.6, 7.8.

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

- Dibutyl adipate, EC 203-350-4;

- Reaction mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate (Dibasicesters, DBE), EC 906-170-0;
- 1,4-dimethyl butanedioate 1,5-dimethyl pentanedioate 1,6-dimethyl hexanedioate, EC 619-131-5;
- Dimethyl glutarate, EC 214-277-2;
- 2-methylpropan-1-ol, EC 201-148-0.

12 You provide the following reasoning for the prediction of toxicological properties: "The toxicity profile of the members (ecotoxicity and human health toxicity and the environmental fate) is consistent. All have low acute toxicity potential, are not sensitising, are mildly irritating to eyes and upper respiratory tract (where vapour pressure allows exposure), are not genotoxic or clastogenic (in vivo) and have minimal systemic toxicity. Data are available predominantly for the methyl esters (individual and mixture), dibutyl adipate and diisobutyl esters (mixture). Within the category, read across is used to cover the higher tier human health toxicity studies predominantly".

13 "Dosing of the diisobutyl esters will result in the release of the acids and isobutanol, therefore read across to the dimethyl esters is considered appropriate since the major hydrolysis products of the dimethyl esters are the corresponding acids. In support of this, data on isobutanol are also provided as isobutanol would be released from the diisobutyl esters once entering the body".

14 Based on your choice of source substances per endpoint, ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effect, and that you complete your approach with data for the non-common biotransformation product. You predict the properties of your Substance to be quantitatively equal to those of the source substance based on an identified trend within the group.

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

0.1.2.1. Missing supporting information to compare properties of the substances(s)

16 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.).

17 Supporting information must include bridging studies to compare properties of the category members.

18 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the substance(s) is necessary to confirm that the 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).

19 You provided several studies on source substances, including 6 in vitro studies, 2 in vivo micronucleus studies, 2 sub-chronic studies, and 4 pre-natal developmental toxicity studies. Specific reasons why these studies cannot be considered reliable are explained further below under the relevant information requirement sections 4, 7 and 8. Thus the data set

reported in the technical dossier does not include relevant, reliable and adequate information for the source substance(s) to support your read-across hypothesis.

20 You provided no study on the target substance relevant to the five adapted information requirements with e.g. lower shorter exposure duration (bridging study).

21 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.

0.1.2.2. Inadequate or unreliable studies on the source substance(s)

22 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) be adequate for the purpose of classification and labelling and/or risk assessment;

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

(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

23 Specific reasons why the studies on the source substance(s) do not meet these criteria are explained further below under the applicable information requirement sections 3-5. Therefore, no reliable predictions can be made for these information requirements.

0.1.3. Conclusion on the read-across approach

24 Based on the 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 and, in the case of cytogenicity, your analogue study has significant reliability issues further addressed under Section 2 below.

25 In your comments, you submitted a new read across justification document. In that document you present a strategy relying on the generation of additional supporting information on the Substance and on the analogue substances ECs 906-170-0, 211-020-6, 936-196-8, 214-277-2 and 203-419-9. ECHA acknowledges your intention. As indicated in your comments, this strategy relies essentially on data, which is yet to be generated, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VII of REACH

1. Growth inhibition study aquatic plants

26 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

1.1. Information provided

27 You have provided:

(i) Growth inhibition study on aquatic plants/algae (ISO 10253, 2009) with the Substance.

1.2. Assessment of the information provided

1.2.1. The provided study does not meet the specifications of the test guideline(s)

28 To fulfil the information requirement, a study must comply with OECD TG 201 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

29 Validity criteria

a) exponential growth in the control cultures is observed over the entire duration of the test;

b) at least 16-fold increase in biomass is observed in the control cultures by the end of the test;

c) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%.

30 Characterisation of exposure

d) for some substances (*e.g.* adsorbing substances), the results may only be expressed based on nominal concentrations if the decrease in measured concentrations of the test substance during the test is not accompanied by a decrease in growth inhibition. If a reduction in growth inhibition is observed, a suitable model describing the decline of the concentration of the test material must be used;

e) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test.

31 Reporting of the methodology and results

f) adequate information on the analytical method (including performance parameters of the method).

32 In study (i):

33 Validity criteria

a-c) you claim that the validity criteria are fulfilled, however there are no raw data to verify the validity criteria.

34 Characterisation of exposure

d) You have expressed the effect values based on nominal concentrations. Since the raw data are not available, it is not possible to verify whether the decrease in measured concentrations of the test substance (under the limit of detection) during the test is accompanied by a decrease of the growth inhibition.

e) You have expressed the effect values based on nominal concentrations. The concentrations of the test material were not within ± 20 % of nominal or measured initial concentration throughout the test.

35 Reporting of the methodology and results

f) on the analytical method adequate information (e.g. performance parameters of the method, LOD, LOQ, column used, program used) is not reported.

36 Based on the above,

- the Substance is difficult to test (considering that the Substance is surface active) and there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, you have expressed the effect values based on nominal concentrations, however the concentrations of the test material decrease throughout the test under the limit of detection of the analytical method. It is not possible to determine whether and to what extent the tested organisms were exposed to the test material and thus the study is not reliable. When the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material over the exposure period.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, there are no raw data to check and confirm that the validity criteria are fulfilled and there is no detailed information on the analytical method used.

37 On this basis, the specifications of OECD TG 201 are not met.

38 Therefore, the information requirement is not fulfilled.

39 In your comments to the draft decision, you agreed to perform the requested study.

1.3. Study design and test specifications

40 The Substance is difficult to test due to the its surface active properties (50.3 mN/m). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2. *In vitro* gene mutation study in bacteria

41 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

2.1. Information provided

42 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* gene mutation study in bacteria (1996) with the source substance dibutyl adipate, EC 203-350-4;

(ii) an *in vitro* gene mutation study in bacteria (1988) with the source substance 1,4-dimethyl butanedioate 1,5-dimethyl pentanedioate 1,6-dimethyl hexanedioate, EC 619-131-5;

(iii) an *in vitro* gene mutation study in bacteria (1985) with the source substance 2-methylpropan-1-ol, EC 201-148-0;

(iv) an *in vitro* gene mutation study in bacteria (1988) with the source substance 2-methylpropan-1-ol, EC 201-148-0.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

43 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.

44 We have identified the following issue(s) with the prediction of toxicological properties.

2.2.2. Inadequate or unreliable studies on the source substance(s)

45 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 be normally performed for a particular information requirement, in this case OECD TG 471. Therefore, the following specifications must be met:

a) the test is 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).

46 In study (ii):

a) the test was performed with the strains TA 98, TA 100, TM 677 (i.e., the strains 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), are missing).

47 In study (iv):

a) the test was performed with the strains TA97, TA 98, TA 100, TA 1535, TA1537 (i.e., the one strain, which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101), is missing).

48 Therefore, the study 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 corresponding OECD TG.

49 Therefore, the information requirement is not fulfilled.

50 In your comments to the draft decision, you agreed to perform the requested study.

2.3. Specification of the study design

51 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

Reasons related to the information under Annex VIII of REACH

3. *In vitro* micronucleus study

52 An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

3.1. Information provided

53 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on the following:

(i) an *in vitro* cytogenicity study in mammalian cells (1996) with the source substance dibutyl adipate, EC 203-350-4, showing positive results with metabolic activation;

(ii) an *in vitro* cytogenicity study in mammalian cells (1987) with the source substance 1,4-dimethyl butanedioate 1,5-dimethyl pentanedioate 1,6-dimethyl hexanedioate, EC 619-131-5;

(iii) an *in vitro* micronucleus study in mammalian cells (2002, secondary literature) with the source substance 2-methylpropan-1-ol EC 201-148-0;

(iv) an *in vivo* micronucleus assay (1987) with the source substance 1,4-dimethyl butanedioate 1,5-dimethyl pentanedioate 1,6-dimethyl hexanedioate, EC 619-131-5;

(v) an *in vivo* micronucleus assay (2001) with the source substance dimethyl glutarate, EC 214-277-2.

54 To support your adaptation, you have also provided the following statement:

(vi) *"A weight of evidence approach evaluating in vitro and in vivo data is therefore needed to assess the mutagenic potency of DBE."*

3.2. Assessment of the information provided

55 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

56 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

57 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude on the corresponding information requirement.

3.2.1. Lack of documentation justifying the weight of evidence adaptation

58 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

59 You have not included a justification for your weight of evidence adaptation which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

60 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation and identified the issue(s) addressed below.

3.2.2. Unreliable sources of information

61 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes:

- Detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells *(in vitro*) or in mammals (*in vivo*).

62 A level of information on these aspects similar to that obtained from *in vitro/in vivo* chromosomal aberration tests (OECD TG 473/OECD TG 475) or *in vitro/in vivo* micronucleus tests (OECD TG 487/OECD TG 474) is required.

63 The sources of information provide relevant information on detection and quantification of chromosomal aberration in cultured mammalian cells. However, these sources of information have the following deficiencies affecting their reliability.

64 The reliability of sources of information (i) to (v) is significantly affected by the deficiency identified and explained under Section 0.1 of the Appendix on Reasons common to several requests. Since statement (vi) relies on the the sources of information (i) to (v), it is by extension also unreliable.

65 In summary, the sources of information (i) to (vi) cover information on the frequency of cells with structural chromosomal aberrations or the frequency of micronuclei in cultured mammalian cells. However, these sources of information have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause cytogenicity.

3.2.3. Conclusion

66 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for *in vitro* chromosomal aberrations/micro-nucleus study in mammalian cells.

67 Based on the above, your adaptation is rejected.

68 Therefore, the information requirement is not fulfilled.

69 In your comments to the draft decision, you agreed to perform the requested study.

3.3. Specification of the study design

70 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the *in vitro* mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the *in vitro* mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations

(aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2).Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro.Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

3.3.1. Assessment of aneugenicity potential

71 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

72 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

4. *In vitro* gene mutation study in mammalian cells

73 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.

4.1. Triggering of the information requirement

74 Your dossier contains an adaptation for an in vitro gene mutation study in bacteria, and an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

75 The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in requests 2 and 3.

76 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.

77 Consequently, you are required to provide information for this information requirement, if the in vitro gene mutation study in bacteria and the in vitro micronucleus study provides a negative result.

4.2. Information provided

78 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) an *in vitro* gene mutation study in mammalian cells (2002) with the source substance dimethyl glutarate, EC 214-277-2.

(ii) a scientific publication (2002) with the source substance 2-methylpropan-1-ol, EC 201-148-0.

4.3. Assessment of the information provided

4.3.1. Read-across adaptation rejected

79 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.

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

4.3.1.1. Inadequate or unreliable studies on the source substance(s)

81 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must have adequate and reliable coverage of the key parameters of the corresponding test method, in this case OECD TG 476 or OECD TG 490. Therefore, the following specifications must be met:

a) at least 4 concentrations are evaluated, in absence and in presence of metabolic activation.

82 In study (ii):

a) the number of tested concentrations that were evaluated in absence and in presence of metabolic activation is not reported.

83 The information provided does not have adequate and reliable coverage of the key parameters of the OECD TG 476/490.

84 Therefore, the information requirement is not fulfilled.

85 In your comments to the draft decision, you agreed to perform the requested study.

4.4. Specification of the study design

86 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.

Reasons related to the information under Annex IX of REACH

5. Long-term toxicity testing on aquatic invertebrates

87 Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

5.1. Information provided

88 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) Justification for data waiving: '*This substance (COASOL) is readily biodegradable and is not considered hazardous to the environment or human health. In accordance with column 2 of REACH Annex IX, long term toxicity testing on aquatic invertebrates (required in section 9.1.5) shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. Since this substance is not classified as hazardous to the environment, no chemical safety assessment is required nor is any additional ecotoxicity testing. Hence, long-term invertebrate testing can be waived for COASOL.*'.

5.2. Assessment of the information provided

5.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

89 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to aquatic invertebrates referred to under Column 1, Section 9.1.5.

90 Your adaptation is therefore rejected.

91 Therefore, the information requirement is not fulfilled.

92 In your comments to the draft decision, you agreed to perform the requested study.

5.3. Study design and test specifications

93 OECD TG 211 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design and test specifications" under request 1.

6. Long-term toxicity testing on fish

94 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

6.1. Information provided

95 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) Justification for data waiving: '*This substance (COASOL) is readily biodegradable and is not considered hazardous to the environment or human health. In accordance with column 2 of REACH Annex IX, long term toxicity testing on fish (required in section 9.1.6) shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. Since this substance is not classified as hazardous to the environment, no chemical safety assessment is required nor is any additional ecotoxicity testing. Hence, long-term testing in fish can be waived for COASOL.*'.

6.2. Assessment of the information provided

6.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

96 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

97 Your adaptation is therefore rejected.

98 Therefore, the information requirement is not fulfilled.

99 In your comments to the draft decision, you agreed to perform the requested study.

6.3. Study design and test specifications

100 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

101 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design and test specifications" under request 1.

7. Sub-chronic toxicity study (90 days)

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

7.1. Information provided

103 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a sub-chronic toxicity study (2000) with the source substance Reaction mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate, EC 906-170-0;

(ii) a sub-chronic toxicity study (1987) with the source substance Reaction mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate, EC 906-170-0.

7.2. Assessment of the information provided

7.2.1. Read-across adaptation rejected

104 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.

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

7.2.1.1. Inadequate or unreliable studies on the source substance(s)

106 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 408/413. Therefore, the following specifications must be met:

a) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) the highest dose level aims to induce toxicity or reach the limit dose.

107 In study (i):

a) there was only one dose level;

b) you do not provide any justification for the dose setting while the highest dose level tested was 400 mg/m^3, which is below the limit dose of the test guideline, and no adverse effects were observed.

108 Therefore, the study 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 corresponding OECD TG.

109 Therefore, the information requirement is not fulfilled.

110 In your comments to the draft decision you state that you want to adapt this information requirement by using a grouping and read-across approach under Annex XI, Section 1.5. You intend to perform "bridging studies on the three substances in the DBE category" as well as on the Reaction Mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate (EC 906-170-0).

111 ECHA acknowledges your intention. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

7.3. Specification of the study design

112 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance. ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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

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

8. Pre-natal developmental toxicity study in one species

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

8.1. Information provided

116 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a pre-natal developmental toxicity study in rats (1995) with the source substance Reaction mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate, EC 906-170-0;

(ii) a pre-natal developmental toxicity study in rabbits (2003) with the source substance dimethyl glutarate, EC 214-277-2;

(iii) a pre-natal developmental toxicity study in rabbits (1995) with the source substance 2-methylpropan-1-ol EC 201-148-0;

(iv) a pre-natal developmental toxicity study in rats (1995) with the source substance 2-methylpropan-1-ol EC 201-148-0.

8.2. Assessment of the information provided

8.2.1. Read-across adaptation rejected

117 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.

118 Therefore, the information requirement is not fulfilled.

119 In your comments to the draft decision you state that you want to adapt this information requirement requirements by using grouping and read-across approach under Annex XI, Section 1.5. You intend to perform "bridging studies on the three substances in the DBE category" as well as on the Reaction Mass of dimethyl adipate, dimethyl glutarate and dimethyl succinate (EC 906-170-0). ECHA acknowledges your intention. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made. You remain responsible for complying with this decision by the set deadline.

8.3. Specification of the study design

120 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

121 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

122 Therefore, the study must be conducted in rats or 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).
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

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. Your EOGRTS testing proposal may be addressed in a separate decision once the information from the sub-chronic toxicity study (90 days) requested in this decision is provided; because the results from the 90-day study are needed for the design of the EOGRTS. Similarly the information requirement for a screening study 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 26 July 2022.

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.

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 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 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]

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.

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

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).