

Helsinki, 20 September 2023

**Addressee(s)**

Registrant(s) of JS\_28473-19-0 as listed in Appendix 3 of this decision

**Date of submission of the dossier subject to this decision**

17 July 2020

**Registered substance subject to this decision ("the Substance")**

Substance name: Diisodecyl sebacate

EC/List number: 249-047-0

**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 **29 September 2025**.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.)
  - a) *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
  - b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).
2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020)).
3. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

4. *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.
5. 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).
6. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

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

7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)
8. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

The reasons for the request(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.

In the requests above, the same study has been requested under different Annexes or for different information requirements.

In the case of the same study requested under different Annexes, this is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided.

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<sup>1</sup> under the authority of Mike Rasenberg, Director of Hazard Assessment

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<sup>1</sup> 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)

Appendix 2: Procedure

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Appendix 4: Conducting and reporting new tests under REACH

## **Appendix 1: Reasons for the request(s)**

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## Reasons common to several requests

### 0.1. QSAR adaptation rejected

1 You seek to adapt the following standard information requirements by applying (Q)SAR approaches in accordance with Annex XI, Section 1.3.:

- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

2 ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

3 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

- (1) the prediction needs to be derived from a scientifically valid model,
- (2) the substance must fall within the applicability domain of the model,
- (3) results need to be adequate for the purpose of risk assessment or classification and labelling, and
- (4) adequate and reliable documentation of the method must be provided.

#### 0.1.1. (Q)SAR for skin sensitisation properties

##### 0.1.1.1. Inadequate documentation of the prediction (QPRF)

4 ECHA Guidance R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint;
- the relationship between the modelled substance and the defined applicability domain;
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

5 You provided the following information about the prediction: You state that the Substance was "predicted not to be a skin sensitiser from its structure using the Danish EPA DB model via the OECD QSAR Toolbox (v.3.0)" and submitted a Toolbox report.

6 However, the information you provided about the prediction lacks the following elements: based on which information the prediction was generated (in vitro, mouse, guinea pig and/or human), details to independently verify that the substance falls within the applicability domain as described in the QMRF of the models, information on analogues and how their predicted and experimental data supports the prediction.

7 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

#### 0.1.2. (Q)SAR for genetic toxicity

*0.1.2.1. Inappropriate measures of robustness of the model*

- 8 The Guidance on IRs and CSA R.6.1.3. states that for (Q)SAR models, to be scientifically valid, i.e. condition (1), they must fulfil the principles listed in the OECD Principles for (Q)SAR validation (ENV/JM/MONO(2007)2). The fourth of these principles requires that a model has appropriate measures of the internal performance (i.e. goodness-of-fit and robustness) and predictivity.
- 9 You use a Toolbox profiler to make a prediction for In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.), In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.), and In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) without measures of internal performance and predictivity of the profiler for the prediction of this endpoint.
- 10 Toolbox profilers are models developed for the purpose of identifying analogues and not to make predictions (as indicated on the official QSAR Toolbox website <https://qsartoolbox.org/features/profiling/>). In absence of measures of internal performance and predictivity, a profiler is not considered a scientifically valid approach to meet this information requirement.

*0.1.3. Conclusion*

- 11 Based on the above, your (Q)SAR adaptations under Annex XI, Section 1.3. are rejected.

*0.2. Read-across adaptation rejected*

- 12 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5.:
- Skin sensitisation (Annex VII, Section 8.3.)
  - *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
  - In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
  - In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

- 13 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.

- 14 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.

- 15 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).

*0.2.1. Predictions for toxicological properties*

- 16 You provide a read-across justification document in IUCLID Section 13/CSR.
- 17 You predict the properties of the Substance from information obtained from the following source substance(s):
- Diethylhexyl sebacate, EC 204-558-8 (source substance 1);

- Diisodecyl adipate, EC 248-299-9 (source substance 2).

18 You provide the following reasoning for the prediction of toxicological properties: "The source and target substances have very similar structures in respect of molar mass and commonality of key functional groups, and the target substance has no novel groups of concern. This, together with the similar expected toxicokinetics behaviour and products (as presented above) supports the read-across validity. In addition, the available data (test and predicted) indicate that the source and target substances have similar physico-chemical, fate and behaviour and (eco)toxicity profiles". Furthermore, you state that "The key structural elements (functional groups) of the target and source compounds are the same: all four contain two ester linkages within a long, saturated alkyl chain. The chemicals have a similar molar mass. It is expected that these would breakdown by hydrolysis to a dicarboxylic acid and two alcohols. The molar masses of the acid and alcohol produced from all four diesters are also similar".

19 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.

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

20 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.).

21 Supporting information must include toxicokinetic information on the formation of the common compound and/or supporting information (bridging studies) to compare properties of the target and source substances.

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

23 For the source substances, you provide the studies used in the prediction in the registration dossier. Apart from those studies, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of genetic toxicity data for the Substance that would confirm that both substances cause the same type of effects.

24 As explained in section 0.1 above, your (Q)SAR adaptations under Annex XI, Section 1.3. are rejected and that information is therefore not useful for read-across.

25 Furthermore, you have not provided any experimental information about the hydrolysis of the Substance nor the source substance(s) to support your claim of similar properties between the substances.

26 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.

*0.2.2. Conclusion*

27 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.

*0.3. Weight-of-evidence adaptation rejected*

28 You have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight-of-evidence):

- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

29 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.

30 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.

31 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.

*0.3.1. Unreliable QSAR adaptations*

32 Section 0.1 of the present Appendix identifies deficiencies of the QSAR adaptations used in your dossier. These findings apply equally to the sources of information relating to QSAR submitted under your weight-of-evidence adaptations.

*0.3.2. Unreliable read-across approach*

33 Section 0.2 of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight-of-evidence adaptations.

34 In spite of these critical deficiencies, ECHA has nevertheless assessed the validity of your adaptation.

35 Your weight-of-evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually.

36 The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in request(s) 1, 2, 4 and 5 below.



## Reasons related to the information under Annex VII of REACH

### 1. Skin sensitisation

37 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

#### 1.1. Information provided

38 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) and by using Annex XI, Section 1.3 (QSAR) based on the following:

- (i) a prediction from Danish EPA QSAR Database via the QSAR Toolbox (v.3.0), 2012.
- (ii) an in vivo skin sensitisation test (OECD TG 406) with an analogue substance diisodecyl adipate (EC 248-299-9), 1970

#### 1.2. Assessment of the information provided

##### 1.2.1. (Q)SAR and read-across adaptations rejected

39 As explained in sections 0.1. and 0.2., your adaptations are rejected.

##### 1.2.2. Weight of evidence adaptation rejected

40 Information that can be used to support a weight of evidence adaptation for the information requirements of Section 8.3 at Annex VII includes similar information to that investigated by the internationally recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation. The key investigations of such test methods address each of the 3 key events of skin sensitisation, either individually or in an integrated approach as follows:

- (1) investigation of cell proliferation in the draining lymph nodes (local lymph node assay), or
- (2) investigation of local responses in animals or humans (guinea pig assays or human studies), or
- (3) investigation of molecular interaction with proteins, inflammatory response in keratinocytes and activation of dendritic cells (*in vitro* and *in chemico* assays).

41 The source of information (ii) provides relevant information, as it investigates predicted properties on skin sensitisation.

42 In the absence of QPRF for source of information (i) covering the model predictions, including the endpoint, you have not demonstrated that this source of information investigates on the key investigations above.

43 Further, the studies have the deficiencies identified in Section 0.1 affecting the reliability of its contribution to the weight of evidence approach.

44 Finally, ECHA agrees that the experimental study (ii) provided is not assignable (reliability score 4).

45 The source of information (ii) investigates predicted properties on skin sensitisation, on investigation of local responses in animals. However, the reliability of this source of information is significantly affected for the reasons developed above.

46 Therefore it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous

properties foreseen to be investigated in the recognised in vitro, in chemico and/or in vivo test methods on skin sensitisation.

47 Therefore, your weight of evidence adaptation is rejected.

*1.2.3. No assessment of potency*

48 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

49 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.2. above), this condition cannot be assessed.

50 Therefore, the information requirement is not fulfilled.

*1.3. Study design*

51 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

52 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

## **2. *In vitro* gene mutation study in bacteria**

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

*2.1. Information provided*

54 You have adapted this information requirement by using Annex XI, Section 1.2. (weight-of-evidence), Annex XI, Section 1.3 (QSAR) and Annex XI, Section 1.5. (grouping of substances and read-across approach) based on the following information:

- (i) an *in vitro* gene mutation study in bacteria (1985) with the source substance Diethylhexyl sebacate (EC 204-558-8);
- (ii) an *in vitro* gene mutation study in bacteria (2002) with the source substance Diisodecyl adipate (EC 248-299-9);
- (iii) QSAR (Toolbox profiler).

*2.2. Assessment of the information provided*

*2.2.1. QSAR and read-across adaptations rejected*

55 As explained in sections 0.1. and 0.2., your adaptations are rejected.

*2.2.2. Weight of evidence adaptation rejected*

56 Relevant information that can be used to support weight-of-evidence adaptation for the information requirement of Annex VII, Section 8.4. includes similar information that is produced by the OECD TG 471 with a design as specified in this decision. OECD TG 471 requires the study to investigate the following key elements: Detection and quantification of gene mutations in bacteria.

2.2.2.1. *Detection and quantification of gene mutations*

57 Sources of information (i) and (ii) investigate gene mutations in bacteria. A Toolbox profiler is not intended to make predictions on hazard and therefore you have not demonstrated that it investigates gene mutations in bacteria.

58 Also, the reliability of these sources of information is significantly affected by the following deficiency:

2.2.2.1.1. *Read-across adaptation rejected*

59 Information from source substance(s) can contribute to weight-of-evidence adaptation only if the read-across is acceptable.

60 As explained in section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

61 Therefore, sources of information (i) and (ii) on analogue substances cannot be used to support your weight-of-evidence adaptation.

62 In addition, the reliability of the source of information (i) is also affected by the following issue:

2.2.2.1.2. *Study (i) not adequate for the information requirement*

63 For the data to be considered adequate, the study you submitted has to meet the requirements of the 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).

64 In study(i):

- b) the test was performed with the strains *S. typhimurium* TA 1535, 1537, 98, 100 (i.e., the strain *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is missing).

65 The information provided does not cover the specification(s) required by the OECD TG 471.

66 Therefore, the provided study cannot be considered a reliable source of information that could contribute to the conclusion on this key parameter investigated by the required study.

67 In summary, the sources of information (i) and (ii) provide relevant information on gene mutations in bacteria. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for an in vitro gene mutation study in bacteria.

68 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for an in vitro gene mutation study in bacteria.

2.2.3. *Conclusion*

69 Based on the above, your adaptations are rejected.

70 Therefore, the information requirement is not fulfilled.

*2.3. Study design*

71 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

**3. Long-term toxicity testing on aquatic invertebrates**

72 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

*3.1. Triggering of the information requirement*

73 In the provided OECD TG 105 (2013), the saturation concentration of the Substance in water was determined to be 95 µg/L.

74 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

*3.2. Information requirement not fulfilled*

75 The information provided, its assessment and the specifications of the study design are addressed under request 7.

**Reasons related to the information under Annex VIII of REACH****4. In vitro micronucleus study**

76 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.

*4.1. Information provided*

77 You have adapted this information requirement by using Annex XI, Section 1.2. (weight-of-evidence), Annex XI, Section 1.3. (QSAR) and Annex XI, Section 1.5. (grouping of substances and read-across approach) based on the following information:

- (i) an *in vitro* mammalian chromosome aberration test (2002) with the source substance Diisodecyl adipate (EC 248-299-9);
- (ii) QSAR (Toolbox profiler).

*4.2. Assessment of the information provided**4.2.1. QSAR and read-across adaptations rejected*

78 As explained in sections 0.1. and 0.2., your adaptations are rejected.

*4.2.2. Weight-of-evidence adaptation rejected*

79 Relevant information that can be used to support weight-of-evidence adaptation for the information requirement of Annex VIII, Section 8.4.2. includes similar information that is produced by the OECD TG 473 or OECD TG 487 with a design as specified in this decision. OECD TG 473/487 require the study to investigate the following key elements:

- a. Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells, including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

*4.2.2.1. Detection and quantification of structural or numerical chromosomal aberrations*

80 Source of information (i) only includes detection and quantification of structural or numerical chromosomal aberrations]. A Toolbox profiler is not intended to make predictions on hazard and therefore you have not demonstrated that it investigates structural or numerical chromosomal aberrations.

81 Also, the reliability of this source of information is significantly affected by the following deficiency:

*4.2.2.1.1. Read-across adaptation rejected*

82 Information from source substance(s) can contribute to weight-of-evidence adaptation only if the read-across is acceptable.

83 As explained in section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

84 Therefore, source of information (i) on an analogue substance cannot be used to support your weight-of-evidence adaptation.

85 In summary, the source of information (i) provides relevant information on structural or numerical chromosomal aberrations. However, this source of information has significant

reliability issues as described above and cannot contribute to the conclusion on the information requirement for an in vitro mammalian chromosomal aberration study or an in vitro mammalian micronucleus study.

86 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for an in vitro mammalian chromosomal aberration study or an in vitro mammalian micronucleus study.

#### 4.2.3. Conclusion

87 Based on the above, your adaptations are rejected.

88 Therefore, the information requirement is not fulfilled.

#### 4.3. Study design

89 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).

##### 4.3.1. Assessment of aneugenicity potential

90 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.

91 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).

## 5. *In vitro* gene mutation study in mammalian cells

92 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.

### 5.1. Triggering of the information requirement

93 Your dossier contains adaptations for an in vitro gene mutation study in bacteria, and adaptations for an in vitro cytogenicity study in mammalian cells or in vitro micronucleus study.

94 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 4.

95 The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro micronucleus study 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.

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

### *5.2. Information provided*

97 You have adapted this information requirement by using Annex XI, Section 1.2. (weight-of-evidence), Annex XI, Section 1.3. (QSAR) and Annex XI, Section 1.5. (grouping of substances and read-across approach) based on the following information:

- (i) an *in vitro* gene mutation study in mammalian cells (2002) with the source substance Diisodecyl adipate (EC 248-299-9);
- (ii) QSAR (Toolbox profiler).

### *5.3. Assessment of the information provided*

#### *5.3.1. QSAR and read-across adaptations rejected*

98 As explained in sections 0.1. and 0.2., your adaptations are rejected.

#### *5.3.2. Weight-of-evidence adaptations rejected*

99 Relevant information that can be used to support weight-of-evidence adaptation for the information requirement of Annex VIII, Section 8.4.2 includes similar information that is produced by the OECD TG 476 or OECD TG 490 with a design as specified in this decision. OECD TGs 476/490 require the study to investigate the following key elements:

- (1) Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.), including data on the frequency of mutant colonies in cultured mammalian cells.

##### *5.3.2.1. Detection and quantification of gene mutations*

100 Source of information (i) includes detection and quantification of gene mutations in cultured mammalian cells. A Toolbox profiler is not intended to make predictions on hazard and therefore you have not demonstrated that it investigates gene mutations in mammalian cells.

101 Also, the reliability of this source of information is significantly affected by the following deficiency:

##### *5.3.2.1.1. Read-across adaptation rejected*

102 Information from source substance(s) can contribute to weight-of-evidence adaptation only if the read-across is acceptable.

103 As explained in section 0.2., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

104 Therefore, source of information (i) on an analogue substance cannot be used to support your weight-of-evidence adaptation.

105 In summary, the source of information (i) provides relevant information on gene mutations in mammalian cells. However, this source of information has significant reliability issues as

described above and cannot contribute to the conclusion on the information requirement for an in vitro gene mutation study in mammalian cells.

106 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for an in vitro gene mutation study in mammalian cells.

#### *5.4. Conclusion*

107 Based on the above, your adaptation is rejected.

108 Therefore, the information requirement is not fulfilled.

#### *5.5. Study design*

109 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.

## **6. Long-term toxicity testing on fish**

110 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

#### *6.1. Triggering of the information requirement*

111 As already explained in request 3, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

112 Therefore, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

#### *6.2. Information requirement not fulfilled*

113 The information provided, its assessment and the specifications of the study design are addressed under request 8.



## Reasons related to the information under Annex IX of REACH

### 7. Long-term toxicity testing on aquatic invertebrates

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

#### 7.1. Information provided

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

(i) Justification: '*According to column 2 of Annex IX of REACH, long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. DIDS is considered readily biodegradable, is unlikely to bioaccumulate and no adverse effects were seen in a reliable short-term toxicity limit test with DEHS on aquatic invertebrates. In addition, exposure of the aquatic compartment is unlikely to occur. Therefore, and based on animal welfare considerations, long-term testing is not considered a high priority for further work.*

#### 7.2. Assessment of the information provided

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

116 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.

117 Your adaptation is therefore rejected.

118 Therefore, the information requirement is not fulfilled.

#### 7.3. Study design

119 The Substance is difficult to test due to the low water solubility (0.095 mg/L) and/or adsorptive properties ( $\log K_{ow} > 6.5$ ). OECD TG 211 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 211. 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.

120 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

121 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (Guidance on IRs and CSA, Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);
- prepare WAFs separately for each dose level (i.e. loading rate) and in a consistent manner.

## 8. Long-term toxicity testing on fish

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

### 8.1. Information provided

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

- (i) Justification: *'According to column 2 of Annex IX of REACH, long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. DIDS is readily biodegradable, unlikely to bioaccumulate and no adverse effects were seen in a reliable short-term toxicity limit test with DEHS in freshwater fish. In addition, exposure to the aquatic compartment is unlikely. Therefore, and considering animal welfare issues, long-term testing is not considered a high priority for further work.'*

### 8.2. Assessment of the information provided

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

124 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.

125 Your adaptation is therefore rejected.

126 Therefore, the information requirement is not fulfilled.

### 8.3. Study design

127 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.).

128 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" under request 7.

## 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**

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 11 August 2022.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

In your comments, you requested an extension of deadline. You indicated that there is low availability of testing labs for ecotoxicity, and that you expect difficulties associated with testing the ecotoxicity of a poorly soluble substance. You did however not provide any documentation from test laboratories to justify the need for an extension of the deadline and therefore the deadline indicated in the draft decision remains. 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.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
████████████████████	████████████████████	██████

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<sup>2</sup>.
- (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

##### (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 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.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance.

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>).

<sup>2</sup> <https://echa.europa.eu/practical-guides>