~~Confidential~~

Helsinki, 1 September 2022

Addressees
Registrant(s) of JS_1187576-41-5_PFAE as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
24/09/2015

Registered substance subject to this decision ("the Substance")
Substance name: 2-Butenedioic acid (2E)-, di-C14-16-alkyl esters
EC number: 695-949-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***8 December 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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)

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

3. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

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

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

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

6. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

7. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats

8. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: EU C.47./OECD TG 210)

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

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

In the requests above, the same study has been 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. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

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

- 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.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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

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

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

5 You have provided a category approach, which is addressed under section 0.1.1 and 0.1.21.2 below, and an analogue approach which is addressed under section 0.1.2 below.

0.1.1. Scope of the grouping of substances (category)

6 You provide a read-across justification document in IUCLID Section 13, and an updated version with the comments on the draft decision.

7 For the purpose of this decision, the following abbreviations are used for the category members:

1) 2-Butenedioic acid (E)-, di-C8- 18-alkyl esters EC 271-880-3
2) Didodecyl fumarate 2-Butenedioic acid (E)-, didodecyl ester, EC 219-280-2
3) 2-Butenedioic acid (2E)-, di-C12-14-alkyl esters, List 938-575-3
4) Ditetradecyl fumarate, 2-Butenedioic acid (E)-, ditetradecyl ester, EC 233-739-4
5) 2-Butenedioic acid (2E)-, di-C14-16-alkyl esters, List 695-949-6

6) 2-Butenedioic acid (E)-, di-C12-18-alkyl esters EC 272-943-8

7) 2-Butenedioic acid (E)-, diC16-18-alkyl esters EC 272-944-3

8) 2-Butenedioic acid (E)-, di-C18-22-alkyl ester, EC 272-945-9

8 You justify the grouping of the substances as: "PFAE fumarate esters have a common metabolic fate […] by which the breakdown of glycol esters results in structurally similar chemicals, the fumaric acid component and the respective alcohol".

9 You define the applicability domain of the "PFAE fumarates category" as: "diesters of the unsaturated dicarboxylic acids: fumaric acid (C4) and aliphatic alcohols with C8-C22 even and linear carbon chains."

10 Furthermore you use information from a source substance outside the category definition, Bis(2-ethylhexyl) adipate (EC 203-090-1) and you have not demonstrated how the category would be relevant to justify the read-across from that substance.

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

0.1.2. Predictions for eco-/toxicological properties

12 You provide a read-across justification document in IUCLID Section 13.

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

1) didodecyl fumarate EC No. 219-280-2
2) bis(2-ethylhexyl) adipate, EC No. 203-090-1
3) 2-Butenedioic acid (E)-, di-C18-22-alkyl esters, EC 272-945-9
4) 2-Butenedioic acid (E)-, ditetradecyl ester, EC 233-739-4

14 You provide the following reasoning for the prediction of toxicological properties: "After oral ingestion, the members of the PFAE fumarates category undergo stepwise hydrolysis of the ester bonds by gastrointestinal enzymes. The respective alcohol as well as the fatty acid is formed. Esters of alcohols and fatty acids undergo esterase-catalysed hydrolysis, leading to the cleavage products fatty alcohol (C8-C22) and fumaric acid (CAS 110-17-8)."

15 For toxicological endpoints, you propose a conservative approach: The "substance didodecyl fumarate EC No. 219-280-2 (CAS No. 2402-58-6) [source substance 1] was selected for testing, because it represents the category member with the shortest fatty alcohol side chain, and consequently with the lowest molecular weight, which is regarded as worst-case approach in terms of hazard assessment of the PFAE fumarates for the local as well as for systemic effects."

16 Furthermore, you claim that: "The toxicological properties show that all category members and the structurally related analogue substance Bis(2-ethylhexyl) adipate [source substance 2] share similar toxicokinetic behaviour (i.e. hydrolysis of the ester bond before absorption followed by absorption and metabolism of the breakdown products) and that the constant pattern consists in a lack of potency change of properties across the category, explained by the common metabolic fate of aliphatic diesters, independently of the chain length of the dicarboxylic acid moiety (C4 unsatd. or C6) and the lengths/branching of the alcohol moiety."

17 You provide the following reasoning for the prediction of ecotoxicological properties: "Fumarates are biotransformed to dicarboxylic acids and the corresponding alcohol component by the ubiquitous carboxylesterase enzymes in aquatic species."

18 For ecotoxicological endpoints, you propose an approach involving interpolation: "available studies cover the outer borders of this category so that the aquatic toxicity endpoints are covered by interpolation (i.e. studies are available for the lower alcohol chain length (C12, C14) and highest alcohol chain length (C18/C22), respectively)."

19 You conclude that "Due to the structural similarities and consistent trend in physico-chemical, toxicological, ecotoxicological properties and toxicokinetic behaviour, the members of the PFAE fumarate group can be considered as a category of substances"

20 We understand that you apply a category approach for the PFAE fumarates for which 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 source substance 1 for toxicological endpoints.

21 We have identified the following issues with the predictions of toxicological properties for the category approach in sections 0.1.2.1 and 0.1.2.3 below.

22 In addition, we understand that you apply an analogue approach for which 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 source substances 1, 3, and 4 for ecotoxicological endpoints and to be based on a worst-case approach from source substance 2 for toxicological endpoints.

23 We have identified the following issues with the predictions of toxicological properties for the analogue approach in sections 0.1.2.2 and 0.1.2.3.

0.1.2.1. Data density of toxicological endpoints

24 Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances".

25 According to the Guidance on IRs and CSA, Section R.6.2.1.5., one of the factors in determining the robustness of a category is the density and distribution of the available data across the category. To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

26 You have provided one combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test and in-vitro genotoxicity studies with source substance 1 as supporting information for your category. You have not provided further similar supporting (bridging) information with any of the other category members.

27 For source substance 2, which is not a category member, you provide the studies used in the prediction in the registration dossier.

28 Information for one category member is not sufficient to establish a trend across the category consisting of seven substances. Furthermore, it cannot be confirmed

that there is no breakpoint in toxicity trend within the given range of chain length across the category. Therefore, the information provided is not sufficient to conclude that toxicological properties are likely to follow a regular pattern across the category.

29 In your comments on the draft decision you state your adaptation of the information requirement according to Annex XI, Section 1.5. You present a strategy relying on the generation of studies to fill all information requirements of category members 1, 2, 4, 5, 7 and 8 (Sections 8.4.1, 8.4.2, 8.4.3, 8.7.1, 8.6.2, 8.7.2, 9.1.2., 9 .1.3., and 9.1.6. from Annexes VII-IX) as requested in their respective draft decisions. These category members shall represent the lower, intermediate and upper range of members of the category and thereby enable interpolating predictions across the category. You argue that the constituent profile of these category members supports your approach, and that no further experimental information on category members (bridging studies) is required to support the predictions for human health. For ecotoxicological information requirements you indicate that further experimental information on long-term toxicity to invertebrates on all category members (bridging studies) will be provided to support the predictions. You indicate your intention to provide this in a future update of your registration dossier.

30 We acknowledge your intentions to improve the (eco)toxicological profile of the Substance and your plans to refine your read-across approach. It relies on data which is yet to be generated. Therefore no conclusion on the compliance can currently be made, because only the future study results will determine whether the (eco)toxicological profiles of the category members are coherent and support your hypothesis. You remain responsible for complying with this decision by the set deadline.

31 The validity of the prediction from source substance 2 is affected by the deficiencies identified in section 0.1.2.2 and 1.2.2.3.

0.1.2.2. Missing supporting information to compare properties of the substances

32 Annex XI, Section 1.5 of the REACH Regulation states that "physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)". For this purpose "it is important to provide supporting information to strengthen the rationale for the read-across" (Guidance on IRs and CSA, Section R.6.2.2.1.f.). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members.

33 Supporting information must include bridging studies to compare properties between the source substance(s) and the Substance.

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

35 For the source substance, you provide the study used in the prediction in the registration dossier. Apart from that study, your read-across justification or the registration dossier does not include any robust study summaries or descriptions

of data for the Substance that would confirm that both substances cause the same type of effects.

36 The provided study with source substance 1 cannot be used as supporting information equivalent to a bridging study with the Substance, because your category approach fails for the reasons set out in section 0.1.2.1.

37 In the absence of such information, you have not established that the category members are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

0.1.2.3. Adequacy and reliability of source study of eco-/toxicological endpoints

38 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 test method referred to in Article 13(3).

39 Specific reasons why the studies on the source substance do not meet these criteria are explained further below under the applicable information requirement section 2. Therefore, no reliable predictions can be made for these information requirements.

40 Related deficiencies are addressed under the corresponding Appendix below.

0.1.3. Conclusion on the read-across approach

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

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

42 In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471 (2020) is an information requirement under Annex VII to REACH (Section 8.4.1).

1.1. Information provided

43 You have adapted this information requirement by using a Grouping of substances and read-across approach based on experimental data from the following substances: bis(2-ethylhexyl) adipate, EC No. 203-090-1, and didodecyl fumarate EC No. 219-280-2.

44 You have provided the following studies performed with these source substances:

1) 2013 Ames test OECD TG 471, with an analogue substance, didodecyl fumarate, EC No. 219-280-2, (CAS No. 2402-58-6)

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

1.2. Assessment of the information provided

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

47 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.

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

1.3. Specification of the study design

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

2. Growth inhibition study aquatic plants

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

2.1. Information provided

51 You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

You have provided the following studies performed with source substances:

1) a study according to OECD TG 201 with source substance 1 (EC 219-280-2)
2) a study according to OECD TG 201 with source substance 3 (EC 272-945-9)
3) a study according to OECD TG 201 and OECD GD 23 with source substance 4 (EC 233-739-4)

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

2.2. Read-across adaptation rejected

53 As explained in Section 0.1 your adaptation based on grouping of substances and

read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

2.2.1. Source studies not adequate for the information requirement

54 As explained under the Section on reasons common to several requsts, the results to be read across must have an adequate and reliable coverage of the key parameters addressed Therefore, the following specifications must be met:

55 Characterisation of exposure

a) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;

2.2.1.1. Information provided

56 Your registration dossier provides the following studies:

57 Characterisation of exposure

a) no analytical monitoring of exposure was conducted for studies 1), 2) and 3); In addition to this, you have not provided a justification as to why the analytical monitoring of exposure concentrations is not technically feasible.

2.2.1.2. Assessment of the information provided

58 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically, because no analytical monitoring has been performed, the exposure concentrations cannot be confirmed.

59 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

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

2.3. Study design and test specifications

61 The Substance is difficult to test due to the low water solubility (water solubility ≥ 0.01 mg/L and <0.05 mg/L) and the high potential for adsorption (Log Koc > 5). 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.

62 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).

63 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.

3. Long-term toxicity testing on aquatic invertebrates

64 Short-term toxicity testing on aquatic invertebrates is an information requirement under Column 1 of Annex VII to REACH (Section 9.1.1.). However, long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

65 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

66 In the provided OECD TG 105 (2014), the saturation concentration of the Substance in water was determined to be ≥ 0.01 mg/L and <0.05 mg/L.

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

3.1. Information provided

68 You have provided an adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. for short-term toxicity testing to aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.

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

3.2. Assessment of the information provided

70 We have assessed this information and identified the following issues:

71 In the absence of information, the information requirement is not fulfilled.

3.3. Study design and test specifications

72 OECD TG 202 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' in Section 2.

Reasons related to the information under Annex VIII of REACH

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

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

4.1. Information provided

74 You have adapted this information requirement by using a Grouping of substances and read-across approach. You have provided the following studies performed with source substances:

1) 2013 MN test OECD TG 476, with source substance EC No. 219-280-2, didodecyl fumarate CAS No. 2402-58-6

75 In the comments to the draft decision, you indicate your intention of adapting this information requirement through grouping and read-across. Please see our detailed reply in section 0.1.

4.2. Assessment of the information provided

76 As explained above in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

4.3. Specification of the study design

77 To fulfil the information requirement for the Substance, both In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

5. In vitro gene mutation study in mammalian cells

78 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

79 The in vitro gene mutation study in bacteria, and in vitro cytogenicity study in mammalian cells and in vitro micronucleus study provided in the dossier is rejected for the reasons provided in sections 1 and 4.

80 The result of the request for information in section 1 and 4 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.

5.1. Information provided

81 You have adapted this information requirement by using a Grouping of substances and read-across approach.

82 You have provided the following studies performed with these source substances:

1) 2013 HPRT test OECD TG 476, with source substance EC No. 219-280-2, didodecyl fumarate CAS No. 2402-58-6

83 In the comments to the draft decision, you indicate your intention of adapting this information requirement through grouping and read-across. Please see our detailed reply in section 0.1.

5.2. Assessment of the information provided

84 As explained above in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

5.3. Specification of the study design

85 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. Short-term repeated dose toxicity (28 days)

86 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

6.1. Information provided

87 You have adapted this information requirement by relying on a Grouping of substances and read-across approach to fulfil the information requirement. You have provided the following studies performed with these source substances:

1) 2013 study according to OECD TG 422 study, with an analogue substance didodecyl fumarate , EC No. 219-280-2, (CAS No. 2402-58-6)

88 In the comments to the draft decision, you indicate your intention of adapting this information requirement through grouping and read-across. Please see our detailed reply in section 0.1.

6.2. Assessment of the information provided

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

90 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 As explained in Section 0.1.2.3, the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 407. Therefore, the following specifications must be met:

a. Haematological and clinical biochemistry tests as specified in paragraphs 30-38 of the test guideline.
b. The oestrus cycle in females at necropsy

91 Your registration dossier provides the study 1 listed above. The following specifications are not according to the requirements of OECD TG 407:

a. Data on haematology and clinical biochemistry findings: incidence and severity with relevant base-line values were not reported .
b. Data on oestrus cycle was missing ;

92 Based on the above, the study 1 does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 407 and this study is not an adequate basis for your read-across predictions.

6.3. Specification of the study design

93 When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1. (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

94 For information on the study design see request for OECD TG 422 below.

7. Screening for reproductive/developmental toxicity

95 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

7.1. Information provided

96 You have adapted this information requirement by using a Grouping of substances and read-across approach.

97 You have provided the following studies performed with these source substances:

1) 2013 OECD 422 study, with source substance, EC No. 219-280-2, didodecyl fumarate CAS No. 2402-58-6

98 In the comments to the draft decision, you indicate your intention of adapting this information requirement through grouping and read-across. Please see our detailed reply in section 0.1.

7.2. Assessment of the information provided

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

100 As explained above in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected.

101 Based on the above, the information you provided do not fulfil the information requirement.

7.3. Specification of the study design

102 A study according to the test method EU B.64/OECD TG 422 must be performed in rats.

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

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

8. Long-term toxicity testing on fish

105 Short-term toxicity testing on fish is an information requirement under Column 1 of Annex VIII to REACH (Section 9.1.3.). However, long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

106 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (Guidance on IRs and CSA, Section R.7.8.5).

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

8.1. Information provided

108 You have provided adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. for short-term toxicity testing to fish but no information on long-term toxicity on fish for the Substance.

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

8.2. Assessment of the information provided

110 In the absence of information, the information requirement is not fulfilled.

8.3. Study design and test specifications

111 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.).

112 OECD TG 203 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' in Section 2.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

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

The compliance check was initiated on 3 May 2021.

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

ECHA took into account your comments and amended the deadline.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 30 months from the date of adoption of the decision to allow time for the necessary coordination by the registrants of the category substances and for development of the suitable analytical measurements and preparation of test solutions for this poorly water soluble substance.

On this basis, ECHA has extended the deadline to 30 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

The deadline of the decision has been exceptionally extended by additional 6 months from the deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

Appendix 3: Addressees of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

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

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. Test methods, GLP requirements and reporting

(1) Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

(2) Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

(3) Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. *Selection of the Test material(s)*

   The Test Material used to generate the new data must be selected taking into account the following:
   a) the variation in compositions reported by all members of the joint submission,
   b) the boundary composition(s) of the Substance,
   c) 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*

   a) 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.
   b) The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

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.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

References to Guidance on REACH and other supporting documents can be found in Appendix 1.

[3] https://echa.europa.eu/manuals