~~Confidential~~

Helsinki, 25 November 2022

Addressees
Registrant(s) of JS_216689-76-8 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
23 August 2020

Registered substance subject to this decision ("the Substance")
Substance name: Oligomerisation products of 2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bisoxirane with acrylic acid and fatty acids, C18-unsatd., dimers and nonanoic acid
EC number: 701-359-2

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 ***2 March 2026***.

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

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

1. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method);

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 gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490);

5. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats;

6. 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.

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 weight of evidence adaptations

1 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation(s) under Annex XI, Section 1.2:

- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.).

2 Your weight of evidence adaptations are based on information obtained from the Substance itself and from analogue substances structurally similar to the Substance.

3 Your weight of evidence approaches have deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

0.1.1. Missing weighing of the sources of information for each information requirement

4 Annex XI, Section 1.2. requires a reasoned justification which explains why information from several independent sources together enable a conclusion on the information requirement. This justification must explain how the individual sources of information are weighted and how all the sources of information together enable a conclusion on each of the key parameters foreseen by the study normally required for the information requirement.

5 According to the Guidance on IRs and CSA, Section R.4, the weight given to the sources of information is influenced by the reliability of the data, consistency of results, nature and severity of effects, and relevance and coverage of the information for the given information requirement. The reliability of the data is strongly linked to the method used to generate the information.

6 Therefore, aspects such as exposure duration, dose-levels used, and the statistical power of the study affect the weight of the individual sources of information.

7 Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be integrated in order to decide whether they together provide sufficient weight to conclude whether the Substance has or has not the (dangerous) property investigated by each of the key parameters foreseen by the study normally required for the information requirement. As part of the overall conclusion, an assessment of the residual uncertainty is also required.

8 You have provided the following justification for the weight of evidence adaptations:

- For the information requirement for in vitro gene mutation in mammalian cells: "The test substance is not considered to be genotoxic, based on the overall negative results from an Ames test and in vitro chromosomal aberration assay conducted with the test substance as well as mouse lymphoma assays available with the read across substances".
- For the information requirement for screening for reproductive/developmental toxicity study: "Based on the available weight of evidence from studies with

BADGEDA (representing major components of the test substance) and/or nonanoic acid (a metabolite of test substance), the test substance is not expected to pose reproductive or development concern. Nevertheless, as a conservative approach, a LOAEL of 100 mg/kg bw/day (based on lower mean absolute and relative prostate weights (without associated histopathology), reduced sperm motility) from the 90-day repeated dose toxicity study with BADGEDA, has been taken forward for hazard assessment".

9 You have not weighted the individual sources of information nor provided a clear and transparent assessment of to which extent the sources of information cover each of the key parameters foreseen by the study normally required for the information requirement.

10 Additional issues related to weight of evidence are addressed under the corresponding information requirements.

Reasons related to the information under Annex VII of REACH

1. Partition coefficient n-octanol/water

11 Partition coefficient n-octanol/water is an information requirement under Annex VII to REACH (Section 7.8).

1.1. Information provided

12 You have provided an OECD (2012) TG 117 study

1.2. Assessment of the information provided

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

1.2.1. The provided study does not meet the information requirement

14 To fulfil the information requirement, a study must comply with OECD TG 117 (Article 13(3) of REACH). Therefore, the following specifications must be met:

15 Technical specifications impacting the sensitivity/reliability of the test:

a) The test material and the reference substances are soluble in the mobile phase in sufficient concentration to allow their detection;

16 Reporting of the methodology and results:

b) The test material and reference substances used are reported, including their purity, structural formula and CAS number;
c) The test conditions are reported, including details on the analytical column, the guard column, the mobile phase, the detection method, the temperature range and pH;
d) Elution profiles (chromatograms), deadtime and how it was measured is provided;
e) Details on the fitted regression line (log k *versus* log K_{ow}), including the correlation coefficient and the confidence intervals, are reported;
f) Details of the calculation of the reported log K_{ow} are provided;
g) For multi-constituent or UVCB substances, which result in an unresolved band(s), upper and lower limits of log K_{ow}, and the area % of each log K_{ow} peak is reported. Alternatively when appropriate, for multi-constituent or UVCB substances which are a group of homologues, the weighted average log K_{ow} (calculated based on single log K_{ow} values and the corresponding are % values for all peaks that contribute to ≥ 5% to the total peak area) is reported;

17 Your registration dossier provides an OECD TG 117 study showing the following:

18 Technical specifications impacting the sensitivity/reliability of the test

a) The concentrations of the test material was not determined experimentally in the mobile phase (solution of 75/25 (v/v) methanol/water);

19 Reporting of the methodology and results

b) The specific details on test material used for the study are not reported.
c) The analytical method used for the quantification of the substance is not described. The specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range are not reported;

d) The elution profiles (chromatograms) and deadtime measurements are not provided;
e) Details on the fitted regression line (log k *versus* log K_{ow}) confidence intervals are not reported;
f) Details of the calculation of the reported log K_{ow} are not provided;
g) The Substance is a UVCB. Neither the upper and lower limits of log K_{ow}, and the area % of each log K_{ow} peak nor the weighted average log K_{ow} (calculated based on single log K_{ow} values and the corresponding are % values for all peaks that contribute to ≥ 5% to the total peak area) were provided.

20 Based on the above, there are several deficiencies that impact the validity of the study and reliability of the provided results.

21 Firstly, you have not provided information on the solubility of the test substance in the mobile phase.

22 Furthermore, you have not described the analytical method used for the quantification of the substance, therefore we cannot verify if the method used is specific enough for the Substance.

23 Secondly, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, for complex UVCBs, for the determination of Kow a defined range of values should be presented, with an indication of the proportion of substance within a given range (e.g., > 90% of components have log Kow in the range 4-5), to allow the significance of these results to be reflected in the risk assessment.

24 However, the Substance is UVCB and you have provided only an individual value for Kow (i.e. the UVCB has been treated as a single component).

25 Consequently, the reported log Kow is considered not reliable.

26 Therefore, the specifications OECD TG 117 are not met.

27 In your comments to the draft decision you indicated your intention to update the robust study summary with additional information.

28 However, neither in your comments nor subsequently did you provide specific information addressing the issues identified above. Therefore, the information provided in your comments does not change the assessment outcome.

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

2. Growth inhibition study aquatic plants

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

2.1. Information provided

31 You have provided an algae growth inhibition study (OECD TG 201) with the Substance.

2.2. Assessment of the information provided

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

2.2.1. The provided study does not meet the information requirement

33 To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH).

34 Therefore, the following specifications must be met:

35 Characterisation of exposure

a) analytical monitoring must be conducted and adequate information on the analytical method must be provided. For UVCBs, chemical specific analysis of the test solution is required to demonstrate attainment of equilibrium and stability during the test. Alternatively, a justification why specific analytical monitoring of exposure concentrations is not technically feasible must be provided;
b) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test;

36 Additional requirements applicable to difficult to test substances

c) if water-accommodated fractions (WAFs) are used, a preliminary study must be conducted to determine that saturation has been achieved;
d) a justification for, or validation of, the separation technique is provided, especially if filtration is used, as it can cause losses due to adsorption onto the filter matrix;

37 Reporting of the methodology and results

e) the method for determination of biomass and evidence of correlation between the measured parameter and dry weight are reported;
f) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form.

38 The Substance is difficult to test since it is a UVCB substance with constituents that have a low water solubility (below 1 mg/L).

39 Your registration dossier provides an OECD TG 201 study showing the following:

a) You have conducted analytical monitoring of exposure concentrations, but you have not provided information on the analytical method used. In particular, the Substance is UVCB and you have not specified whether specific analytical monitoring was conducted;

b) you have expressed the effect values based on mean measured concentrations;

40 Additional requirements applicable to difficult to test substances

c) WAFs were used and you have not conducted a preliminary study to determine that saturation has been achieved;

d) The test solutions used to prepare the loading rates of 1.0, 10 and 100 mg/L were stirred for a 1-hour period followed by a 0.5-hour settlement period. The Water Accommodated Fractions (WAFs) were subsequently siphoned and used as test solutions. You have not provided a justification for this separation method and information on the removal of suspended undissolved fractions;

41 Reporting of the methodology and results, needed to assess the validity of the study

e) The method used to determine algal biomass is not reported;

f) Tabulated data on the algal biomass determined daily for each treatment group and control are not reported.

42 Based on the above, there are several deficiencies that impact the validity of the study and reliability of the provided results. Firstly, you have not provided information on any of the criteria needed to verify if the validity criteria were fulfilled. Secondly, the Substance is

difficult to test and there are critical methodological deficiencies resulting in the rejection of the study results. Since the Substance is UVCB with poorly water soluble constituents, difficulties in achieving and maintaining test concentrations can be expected. However, you have not justified nor demonstrated that the WAF preparation allowed achieving maximum dissolved concentrations. In addition, you have not specified the method used for analytical monitoring, therefore we cannot verify if chemical specific analysis was conducted, which is required for UVCBs to demonstrate attainment of equilibrium and stability during the test. In the absence of information on chemical specific analysis, you have not demonstrated that the reported effect values based on measured concentrations are reliable.

43 Therefore, the requirements of OECD TG 201 are not met.

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

2.3. Study design and test specifications

45 The Substance is difficult to test since it is a UVCB substance and has constituents with low water solubility (< 1 mg/L). 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.

46 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.

47 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.

48 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.

49 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).

50 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.

51 In your comments to the draft decision you agree to perform the requested study.

3. Long-term toxicity testing on aquatic invertebrates

52 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.

3.1. Triggering of the information requirement

53 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).

54 For the purpose of aquatic toxicity testing, most water solubility methods are not suitable to accurately determine water solubility information on a whole UVCB substance. In such cases, existing empirical information of physicochemical data for major (i.e. predominant) or key (i.e. toxicologically significant) constituents can be used (OECD GD 23).

55 The Substance is a UVCB and you have provided a water solubility study (OECD TG 105/EU Method A.6), where the saturation concentration of the Substance in water was determined to be 10.2 mg/L based on analysis of total organic carbon (TOC).

56 In addition, you have provided short-term toxicity to fish and to aquatic invertebrates studies (OECD TG 202 and 203 respectively) where the analytical monitoring results demonstrate that your UVCB Substance contains constituents with water solubility below 1 mg/L. The measured concentration of the test substance in the samples taken from the water accommodated fractions (WAF) prepared at 100 mg/L (nominal loading) was about 0.16 mg/L at test start in both studies.

57 The provided water solubility study is not suitable to determine water solubility information for the UVCB Substance due to the following. For reliable water solubility results, studies must comply with OECD TG 105/EU Method A.6, which requires to use a substance-specific method for analytical determinations (e.g. gas or liquid chromatography, titration, photometry, voltammetry). In the provided water solubility study (OECD TG 105/EU Method A.6), the method of analysis is Total Organic Carbon (TOC), which is not substance-specific since it measures the total amount of dissolved carbon.

58 Therefore, the experimentally determined water solubility of 10.2 mg/L cannot be used to conclude on the water solubility of the UVCB Substance.

59 However, the results of the quantitative analyses from the highest loading of 100mg/L prepared with the Substance for the short term toxicity tests for fish and aquatic invertebrates show that measured concentrations at test start were below 1 mg/L, hence they confirm a water solubility below 1 mg/L for some (if not all) of the constituents,.

60 Based on the above, the Substance is considered as poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

3.2. Information provided

61 You have provided a short-term toxicity study on aquatic invertebrates (OECD TG 202) but no information on long-term toxicity on aquatic invertebrates for the Substance.

3.3. Assessment of the information provided

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

63 In the absence of information on long-term toxicity on aquatic invertebrates, this information requirement is not fulfilled.

3.4. Study design and test specifications

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

65 In your comments to the draft decision you agree to perform the requested study.

Reasons related to the information under Annex VIII of REACH

4. In vitro gene mutation study in mammalian cells

66 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

4.1. Triggering of the information requirement

67 Your dossier contains negative results for both an Ames test and an *in vitro* cytogenicity study.

68 Therefore, the information requirement is triggered.

4.2. Information provided

69 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using a weight of evidence approach based on the following experimental data:

(i) *In vitro* gene mutation study in bacteria (2011), performed with the Substance;

(ii) *In vitro* cytogenicity study in mammalian cells (2011), performed with the Substance;

(iii) *In vitro* gene mutation study in mammalian cells with analogue substance (2010), performed with the analogue substance DGEBADA, EC: 500-130-2;

(iv) *In vitro* gene mutation study in mammalian cells (2013) performed with the analogue substance nonanoic acid, EC 203-931-2.

70 You conclude from this information that "*The test substance is not considered to be genotoxic, based on the overall negative results from an Ames test and in vitro chromosomal aberration assay conducted with the test substance as well as mouse lymphoma assays available with the read across substances*".

4.3. Assessment of the information provided

71 As explained in Sections 0.1 of the Reasons common to several request above, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

72 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.3 at Annex VIII includes similar information that is produced by the OECD TGs 476/490. The OECD TGs 476/490 investigate the detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) in cultured mammalian cells including data on the frequency of mutant colonies.

73 The sources of information (i) and (ii) do not provide relevant information on the detection and quantification of gene mutations in cultured mammalian cells and they cannot contribute to your weight of evidence.

74 More specifically, the source of information (i) provides information on the detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria

and the source of information (ii) provides information on the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells.

75 The sources of information (iii) and (iv) provide relevant information on the detection and quantification of gene mutations in cultured mammalian cells but have the following deficiencies affecting the reliability of their contribution to the weight of evidence approach.

4.3.1. Reliability of the contribution of the information on analogue substances

76 ECHA understands that you use data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to reliably contribute to the weight of evidence approaches, it would have to meet the requirements for Grouping of substances and read-across approaches.

77 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used.

78 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.

79 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).

80 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).

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

82 To predict the genotoxicity toxicity properties of the Substance you use information on the following analogue substances:

- 4,4'-isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, esters with acrylic acid' (DGEBADA; EC: 500-130-2);
- Nonanoic acid (EC: 203-931-2).

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

84 You state that DGEBADA and the target substance contains [redacted]% identical constituents. More specifically, "*The constituents* [redacted] *are all present in both target and source substances, although in different ratios."*

85 Furthermore, you state that *"The additional constituents of the target substance -* [redacted] *- share the same key functional groups as BADGEDA, including acrylate, carboxylic acid ester, ether, alkene and aryl groups*".

86 Therefore, *"all the constituents of both target and source substances share the same key functional groups, including acrylate, carboxylic acid ester, ether, alkene and aryl group" therefore they "also share the same structural alerts indicative of similar reactivity of both the substances*".

87 You claim that the common constituents of the Substance and the source substance are predicted to "*give rise to the same type of metabolites, including acrylic acid*" and the additional constituents of the Substance are predicted to additionally form nonanoic acid (EC 203-931-2) for which there are literature data showing "an overall low systemic toxicity".

88 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.

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

4.3.1.1. Source studies do not cover the composition of the Substance

90 Hazard information can be obtained from tests conducted with the Substance or from the integration of information on the individual constituents of the Substance as part of a constituent-based approach (Guidance on IRs and CSA, Section R.6.2.2.1.).

91 Whenever a constituent-based approach is applied, the assessment must cover each relevant constituent included in the composition of the Substance to ensure that a reliable prediction can be made.

92 In case certain constituents are considered not to be relevant for the hazard assessment, a justification must be provided

93 You have provided an OECD TG 476 study (study iii) with the analogue substance DGEBADA (EC 500-130-2) to cover about [redacted]% of the composition of the Substance.

94 In addition, you state that the additional constituents of the Substance, which represent the [redacted]% of its composition (i.e. [redacted]), are predicted to give rise to the same metabolites as BADGEDA as well as to nonanoic acid, upon ester hydrolysis. To cover this part of the composition of the Substance you have provided a study (study (iv)) conducted with nonanoic acid; EC: 203-931-2.

95 You base your prediction of metabolism on QSAR Toolbox simulations which predicts metabolism by the rat liver. However, no information is provided on the rate of hydrolysis.

96 Only if instant and complete hydrolysis of the parent substances ([redacted]) are demonstrated, the contribution of the parent does not need to be considered in the overall weight of evidence conclusion. As you have not demonstrated how fast and complete is the hydrolysis, the potential contribution of the parent is not currently covered.

97 In addition, ECHA notes that due to the methodological deficiencies of study (iv), explained below, this study cannot reliably contribute to your weight of evidence adaptation.

98 Based on the above, ECHA concludes that the information provided does not cover 30% of the composition of the Substance.

99 Therefore, no reliable conclusions on the hazardous properties of the Substance as a whole can be derived.

4.3.1.2. Methodological deficiencies of experimental study (iv)

100 The evaluation of the reliability of the contribution of each relevant line of information to the weight of evidence approach includes an assessment of each source of information against the specifications of the test guideline followed.

101 Study (iv) is reported as mouse lymphoma forward mutation assay and has been performed to test protocol similar to the OECD TG 476. This test guideline requires that:

a) data on the cytotoxicity and the mutation frequency for the treated and control cultures are reported;
b) a positive control must be included in the study.

Study (iv) reports positive results with metabolic activation. You state that since "*This*

occurred only in the presence of increasing moderate to severe cytotoxicity and small colony development [….] it was concluded that the results do not reflect intrinsic mutagenicity".

However, you did not provide any data on the cytotoxicity and the mutation frequency for the treated and control cultures, therefore, no independent conclusion on the genotoxicity properties of the source substance can be made.

In addition, no positive control is specified, therefore, the effective performance of the assay is not demonstrated.

Based on the above, the results obtained from the study (iv) cannot be considered as reliable.

4.3.1. Conclusion on the weight of evidence

102 Taken together, the sources of information as indicated above, provide relevant information on the detection and quantification of gene mutations in mammalian cells.

103 However, information provided only covers [redacted]% of the composition of the Substance and there is no reliable information provided to cover the other [redacted]% of the composition of the Substance.

104 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 a study conducted according to the OECD TGs 476/490.

105 On this basis, your adaptation is rejected and the information requirement is not fulfilled.

4.4. Specification of the study design

106 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.

107 In your comments to the draft decision you agree to perform the requested study.

5. Screening for reproductive/developmental toxicity

108 A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard 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. There is no information available in your dossier indicating that your Substance may be a developmental toxicant

5.1. Information provided

109 While you have not provided a specific legal reference for your adaptation of this information requirement, ECHA understands that you have adapted this information requirement by using a weight of evidence approach based on the following experimental data:

(i) Combined repeated dose toxicity study and screening for reproductive/developmental toxicity test (2010), performed with the analogue substance DGEBADA; EC 500-130-2;

(ii) Screening for reproductive/developmental toxicity study (2007), performed with the analogue substance heptanoic acid, EC 203-931-2;

(iii) Sub-chronic (90-day) repeated dose toxicity study (2015), performed with the analogue substance DGEBADA, EC 500-130-2.

110 You conclude that "*Based on the available weight of evidence from studies with BADGEDA (representing major components of the test substance) and/or nonanoic acid (a metabolite of test substance), the test substance is not expected to pose reproductive or development concern. Nevertheless, as a conservative approach, a LOAEL of 100 mg/kg bw/day (based on lower mean absolute and relative prostate weights (without associated histopathology), reduced sperm motility) from the 90-day repeated dose toxicity study with BADGEDA, has been taken forward for hazard assessment*".

5.2. Assessment of the information provided

111 We have assessed this information and identified the following issues.

112 As explained under section 0.1, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

113 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Section 8.7.1. at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. The following aspects have to be covered: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

114 We have assessed the individual sources of information with regard to relevance and reliability and identified the following issue(s):

5.2.1. Aspect 1) Sexual function and fertility

115 Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

116 The sources of information (i) and (ii) provide relevant information on sexual function and fertility.

117 The source of information (iii) provides limited information on sexual function and fertility. More specifically, it provides information only on oestrous cyclicity and sperm parameters and it does not inform on mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility

118 In addition, these sources of information have deficiencies affecting their reliability:

119 The reliability of sources of information (i) and (iii) is limited to the constituents covered; i.e. about [redacted]% of the composition of the Substance (see section 4.3.1.).

120 ECHA notes that the identity of the test material for study (ii) is unclear. According to the read-across justification document it is heptanoic acid. In IUCLID the study record identifies the test material as nonanoic acid, although the endpoint conclusion states that rats were administered the read-across substance heptanoic acid. Two scenarios emerge depending on what the test material is:

121 1) - If the test material is heptanoic acid then ECHA understands that you have provided this information in order to predict the contribution of the metabolite nonanoic acid, i.e. using heptanoic acid as a short chain analogue for nonanoic acid.

122 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 a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).

123 You have not provided documentation or any other explanation how the properties of how the properties of nonanoic acid as a metabolite of the Substance may be predicted from heptanoic acid.

124 In the absence of such information ECHA cannot verify that the reproductive/developmental properties of your Substance can be reliably predicted from the data on the analogue substance heptanoic acid.

125 Therefore, data on heptanoic acid does not contribute to the weight of evidence.

126 2) - If the test material is nonanoic acid then the deficiencies identified in Section 4.3.1. applies equally for this information requirement; i.e. [redacted]% of the composition of the Substance is not covered by the sources of information.

127 Regardless of which test material used, there is an additional issue which significantly affects the reliability of the source of information (ii).

128 Investigations/specifications in an OECD TG 421 study include:

a) body weights are measured at least weekly;

b) food consumption is measured at least weekly;

c) the nature, severity, and duration of clinical signs observed daily are reported;

d) thyroid hormone levels are measured;

e) terminal organ and body weights are reported;

f) gross pathology of reproductive organs is performed, and the presence or absence, incidence and severity of abnormalities is evaluated;

g) histopathology of reproductive organs and tissues is performed, and the presence or absence, incidence and severity of abnormalities is evaluated.

129 The study (ii) is described as a Secondary source: Screening-level hazard characterization: C7 to C9 aliphatic aldehydes and carboxylic acids category (US EPA, 2007).

a to g) The study reports a LOAEL at 200 mg/kg/day. However, data on the parameters listed above (including incidence and severity) are missing. Also body weights and body weight changes are missing.

130 Based on the current information is not possible to independently assess to what extent the OECD TG 421 was followed nor independently assess the results of the study.

5.2.2. Aspect 2) Toxicity to offspring

131 Information on pre- and perinatal developmental toxicity reflected by litter sizes, post-implantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

132 The sources of information (i) and (ii) provide relevant information on toxicity to offspring; however the reliability issues identified for aspect 1) equally applies for this aspect.

133 The source of information (iii) does not provide information on toxicity to offspring.

5.2.3. Aspect 3) Systemic toxicity

134 Information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

135 The studies from (i) to (iii) provide relevant information on systemic toxicity.

136 However, the reliability issues identified for aspect 1) equally applies for this aspect.

137 Based on the above, it is not possible to independently assess to what extent this source of information contributes to the weight of evidence.

5.2.4. Conclusion on the weight of evidence

138 Taken together, the sources of information as indicated above, provide relevant information on the three aspects: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

139 However, the information provided only covers [redacted]% of the composition of the Substance and there is no reliable information provided to cover the other [redacted]% of the composition of the Substance.

140 Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether the Substance has or has not the particular dangerous properties foreseen to be investigated in a study conducted according to the OECD TGs 421.

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

5.5. Specification of the study design

142 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

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

144 In your comments to the draft decision you agree to perform the requested study.

6. Long-term toxicity testing on fish

145 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.

6.1. Triggering of the information requirement

146 You have provided information which demonstrate that the Substance includes constituents that are poorly water soluble, as explained in section "2.1 Triggering of the information requirement" under Request 2.

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

6.2. Information provided

148 You have provided a short-term toxicity on fish study (OECD TG 203) but no information on long-term toxicity on fish for the Substance.

6.3. Assessment of the information provided

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

150 In the absence of information on long-term toxicity on fish, this information requirement is not fulfilled.

6.4. Study design and test specifications

151 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.).

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

153 In your comments to the draft decision you agree to perform the requested study.

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 23 August 2021.

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

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

Deadline to submit the requested information in this decision

In the comments on the draft decision, you requested an extension of the deadline from 12 to 36 months from the date of adoption of the decision. To justify the additional time needed for aquatic toxicity testing, you stated that due to the low water solubility and UVCB nature of the Substance, you "*may need several pre-tests to define the right set-up of the study design. Also developing a good and reliable analytical method will be a challenge, and hence time consuming*". In addition, you pointed out to the limited capacity of the testing laboratories and provided information from three CROs indicating that, based on the current capacity of the laboratories, 36 months are needed to perform and submit the studies.

Based on the documentary evidence provided, ECHA has agreed with your request for a deadline extension and has extended the deadline to 36 months.

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

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

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

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

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

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

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

Appendix 4: Conducting and reporting new tests for REACH purposes

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

1.1. Test methods, GLP requirements and reporting

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

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

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

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

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

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:
- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier
- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

[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