~~Confidential~~

Helsinki, 22 June 2022

Addressees
Registrant(s) of JS_isostearyl alcohol as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
06/05/2013

Registered substance subject to this decision ("the Substance")
Substance name: Isooctadecan-1-ol
EC number: 248-470-8

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 ***30 May 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) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102

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 also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

4. In vitro 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. 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

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

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

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

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

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

11. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; 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 seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Long-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2)

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

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

4 Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

Predictions for (eco)toxicological properties

5 You have provided a read-across justification document in section 1.4 of your Chemical Safety Report (CSR) and in the endpoint summary under 7.8 Toxicity to reproduction and under 6.1.2 Long-term toxicity to fish in IUCLID.

6 You read-across between the Substance as target substance and the following structurally similar substances as source substances:

- Source substance 1: octadecan-1-ol, EC No. 204-017-6 (CAS No. 112-92-5) for toxicity to reproduction
- Source substance 2: pentadecanol, branched (EC No. not specified) for long-term toxicity to fish

7 You have provided the following reasoning for the prediction of (eco)toxicological properties:

- Structural similarity: you consider that the constituents of the Substance are structurally similar, "incorporating an alcohol functional group on an alkyl chain, with C-numbers in the range C14-C20 (predominantly C16-C18)". You indicate that the majority of the constituents are branched "at the tail end of the chain (at or beyond the 6-position)" and that the side branches are "predominantly methyl groups, some ethyl branching is suspected". You conclude that "the significant majority of the composition by weight is either linear or falls within the Soap and

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

Detergent Association (SDA) established definition of 'essentially linear" and that "the constituents of the substance represent members of homologous series of increasing carbon number".

- Similarity in (eco)toxicological properties: based on information on "many analogous structures, particularly n-alcohols with fully linear chains of the same carbon number" you derive that the properties of these substances are driven by their low solubility in water, low vapour pressure, and high partition coefficient associated with the large alkyl group. You consider that "In these terms the properties of linear and branched structures of equivalent carbon number are demonstrated (based on reliable experimental results or property prediction) to be consistent or equivalent. More broadly, the substances generally possess similar physicochemical properties and are readily biodegradable. Based on structure, the initial steps of the metabolic pathways (both bacterial and in vivo mechanisms) would be the same for linear and branched structures. No structural features that might indicate a specific mode of toxic action are present."

8 Based on these elements you propose that "properties would be broadly similar across the linear and essentially linear alcohols in the range C14-C20 within the compositional range defined in Section 1.2"

9 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substances.

10 ECHA notes the following shortcomings with regards to predictions of (eco)toxicological properties.

0.1.1. Missing supporting information: Toxicological properties

11 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

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

14 In your read-across justification you have identified the structural differences between the constituents of the Substance. You highlight that these constituents vary in their alkyl chain length and in their linear or branching nature. Despite these structural differences, you consider that all the constituents of the substance can be regarded as "essentially linear" and that all the constituents of the Substance, when considered in isolation, have similar properties.

15 As you point out in your read-across justification, the Substance is predominantly composed of branched constituents with [redacted] representing more than [redacted] of

its composition. Other constituents of the Substance include [redacted].

16 The source substance that you use in your read-across adaptation is octadecan-1-ol, EC No. 204-017-6 (CAS No. 112-92-5), a linear alcohol constituent of the Substance.

17 You claim that as a result of similarities in physicochemical properties, in molecular weight and in claimed similarity in metabolic pathways, all the constituents of the Substance, when considered in isolation, have similar properties. You state that "both trends relating to change in chain length, and consistency across all analogous substances, are evident for different properties". However, you have not provided information supporting these statements.

18 While the source substance provides information on the contribution of this [redacted] constituent to the properties of the Substance, you have not provided any information to support your assumption that the information on this source substance can be predictive of the properties of the constituents of shorter carbon chain length and/or of branched constituents which are part of the composition of the Substance.

19 For the reasons presented above, you have not established that the properties of the Substance containing branched and linear constituents can be predicted from information on the source substance 1. There is no supporting information to explain why the structural differences between the source substance 1 and the other constituents of the Substance do not influence toxicokinetic and toxicodynamic properties of the Substance.

20 In the absence of such information, you have not established that the Substance and the source substance 1 are likely to have similar properties. Therefore, you have not provided sufficient information to support the rationale for your read-across adaptation.

0.1.2. Missing supporting information: Ecotoxicological properties

21 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

23 As indicated under section 0.1 above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

24 In your read-across justification you have identified the structural differences between the constituents of the Substance. You highlight that these constituents vary in their alkyl chain length and in their linear or branching nature. Despite these structural differences, you consider that all the constituents of the substance can be regarded as "essentially linear" and that all the constituents of the Substance, when considered in isolation, have similar properties.

25 As you point out in your read-across justification, the Substance is predominantly composed of branched constituents with [redacted] representing more than [redacted] of

its composition. Other constituents of the Substance [redacted].

26 You claim that as a result in similarities in physicochemical properties, in molecular weight and in claimed similarity in metabolic pathways, all the constituents of the Substance, when considered in isolation, have similar properties. You state that "both trends relating to change in chain length, and consistency across all analogous substances, are evident for different properties". However, you have not provided relevant information supporting these statements.

27 You use pentadecanol, branched as source substance, an alcohol with an uneven numbered carbon chain that is not part of the composition of the Substance.

28 You provide a supporting study record in which you state that "The C16, C18 and C20 constituents of the substance has been estimated by expert judgement to be non-toxic at the limit of solubility." You base your statement on indications "that no toxicity is observed at the limit of solubility with alcohols with carbon chain lengths ≥C15." You provide as an attachment to this statement the publication 'Environmental properties of long-chain alcohols, Part 2: Structure–activity relationship for chronic aquatic toxicity of long-chain alcohols' by Schaefers et al., 2009.

29 ECHA understands that you intend to use this information to support your read-across for the endpoint long-term toxicity to fish and has assessed it in this regard.

30 Schaefers et al. (2009) provides information on long-term toxicity to daphnids with linear alkyl alcohols of the carbon chain lengths C10, C12, C14 and C15. You did not justify how the provided data informs on the long-term toxicity to fish. Therefore, this information is considered not relevant to support your read-across approach on this endpoint.

31 You have not provided any information to support your assumption that the information on the source substance 2 can be predictive of the properties of the constituents of longer and even numbered carbon chain length and/or of linear constituents which are part of the composition of the Substance.

32 For the reasons presented above, you have not established that the properties of the Substance containing only even numbered, branched and linear constituents can be predicted from information on the source substance 2. There is no supporting information to explain why the structural differences between the source substance 2 and the constituents of the Substance do not influence toxicokinetic and toxicodynamic properties and/or bioavailability of the Substance.

33 In the absence of such information, you have not established that the Substance and the source substance 2 are likely to have similar properties. Therefore, you have not provided sufficient information to support the rationale for your read-across adaptation.

0.1.3. Adequacy and reliability of source studies: Toxicological properties

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

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;
- cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

35 Specific reasons why the studies on the source substance 1 do not meet these criteria are explained further below under the applicable information requirement section 9. Therefore, no reliable predictions can be made for this information requirement.

Conclusions on the read-across approach

36 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

0.2. Assessment of weight of evidence adaptations

37 You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- 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.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Growth inhibition study aquatic plants (algae), (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

38 Your weight of evidence adaptations are based on information obtained from the Substance itself, constituents of the Substance and/or analogue substances structurally similar to constituents of the Substance. The details of the set of information provided for each of the information requirements listed above are provided in the endpoint-specific sections of this document.

39 Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Section, before assessing the specific standard information requirements in the following Sections.

40 Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

41 According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

42 Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

43 You have provided respective endpoint summaries in your dossier for genotoxicity, repeated-dose toxicity, toxicity to algae and long-term toxicity to aquatic invertebrates. In those summaries you briefly present each of the sources of information, describe the results

and conclude that this information can be used as WoE to predict the (eco)toxicological properties of the Substance for the above-mentioned endpoints.

44 Whilst these endpoint summaries can be regarded as attempt of integrated summaries of the data sets, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

45 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Sections below.

46 These issues identified below are essential for all the information requirements in which you invoked a weight of evidence.

Reliability of the contribution of the information on analogue substances

47 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.

48 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).

49 Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[4] and related documents[5, 6].

50 You have provided the justification for using information on analogue substances in section 1.4 of your Chemical Safety Report (CSR) and in the respective endpoint summaries in IUCLID, as described under section 0.1 above.

ECHA understands that your justification for using information on analogue substances in your weight of evidence approach is based on the assumption that the structurally similar substances cause the same type of effect(s).

51 You predict the properties of the Substance:

1) to be quantitatively equal to those of the source substances for the endpoints listed above, except for long-term toxicity to aquatic invertebrates

2) based on a worst-case approach for long-term toxicity to aquatic invertebrates

52 You consider that the set of information obtained from the Substance, some individual constituents of the Substance and/or from structurally similar linear alcohols taken together are adequate to predict the properties of the Substance containing branched and linear constituents of various carbon chain length and to fulfil the corresponding information requirements.

[4] ECHA Guidance R.6
[5] Read-Across Assessment Framework (RAAF)
[6] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

53 ECHA notes the following shortcomings with regards to the reliability of the contribution of the information of the analogue substances to your weight of evidence adaptations.

0.2.1. Missing supporting information: Toxicological properties

54 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

55 Supporting information must include bridging studies to compare properties of the Substance and of the analogue substances.

56 As indicated above, your justification for using information on analogue substances in your weight of evidence approach is based on the assumption that the structurally similar substances cause the same type of effect(s).

57 In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance defined as the set of constituents included in its composition as reported in section 1.2 of the IUCLID dossiers, individual constituents of the Substance and/or from structurally similar linear alcohols is necessary. This is to confirm that the structural differences between the constituents of the Substance and the analogue substances used in the weight of evidence approach do not lead to differences in the properties between these substances.

58 This is also necessary to ensure that the contribution of all the constituents of the Substance to the properties of the Substance are considered.

59 In your justification for using information on analogue substances in your weight of evidence approach, you have identified and characterised structural differences between the constituents of the Substance. You highlight that these constituents vary in their alkyl chain length and in their linear or branching nature. Despite these structural differences, you consider that all the constituents of the substance can be regarded as "essentially linear". You indicate that as a result in similarities in physicochemical properties, in molecular weight and in claimed similarity in metabolic pathways, all the constituents of the Substance and the analogue substances used in your weight of evidence adaptation, when considered in isolation, have similar properties.

60 All the lines of information used in your weight of evidence adaptation, other than those obtained from the Substance itself and from the in vitro gene mutation study in mammalian cells obtained on 2-ethylhexan-1-ol, are derived from linear alcohols.

61 Some of these linear alcohols i.e. [redacted] are constituents of the Substance. The other lines of information are obtained from linear alcohols of carbon chain length which are either longer or shorter than the carbon chain length of the constituents of the Substance.

62 The lines of information obtained from the constituents of the Substance provide information on the properties of these specific constituents, to the extent of the investigations conducted in the corresponding lines of information. Since these lines of information address the properties of constituents of the Substance, they can directly contribute to a weight of evidence approach intended to predict to the relevant properties of the Substance. However, the available information on the constituent(s) of the Substance is not sufficient on its own to predict the properties of the Substance in that it does not address the contribution of the other constituents to the properties of the Substance.

63 The other lines of information are obtained from analogue substances which are not part of the composition of the Substance but are linear alcohols of carbon chain length which are either longer or shorter than the carbon chain length of the constituents of the Substance. You consider that the information from these analogues can be used to predict the properties of the constituents of the Substance based on similarities in their physico-chemical properties and molecular weights only. You do not provide information to support your claims associating the intrinsic physico-chemical properties of these analogue substances with similarities in toxicological properties between these analogue substances and the constituents of the Substance.

64 Furthermore, while you consider that all the constituents of the Substance can be considered as "essentially linear", you have not provided information to support your assumption that the information on linear alcohols can be predictive of the properties of the branched constituents which are part of the composition of the Substance.

65 As presented above, you have not provided supporting information to explain why the structural differences between these analogue substances and the constituents of the Substance do not influence the toxicokinetic and toxicodynamic properties of the Substance.

0.2.2. Missing supporting information: Ecotoxicological properties

66 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

67 Supporting information must include bridging studies to compare properties of the Substance and of the analogue substances.

68 As indicated above, your justification for using information on analogue substances in your weight of evidence approach is based on the assumption that the structurally similar substances cause the same type of effect(s) for the prediction of toxicity to algae and that the analogue substance 1-tetradecanol, linear constitutes a worst-case for the prediction of the long-term effects to aquatic invertebrates of the Substance.

69 In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance defined as the set of constituents included in its composition as reported in section 1.2 of IUCLID, individual constituents of the Substance is necessary. This is to confirm that a conservative prediction of the properties of the Substance from the data on the analogue substances can be done.

70 This is also necessary to ensure that the contribution of all the constituents of the Substance to the properties of the Substance are considered.

71 In your justification for using information on analogue substances in your weight of evidence approach, you have identified and characterised structural differences between the constituents of the Substance. You highlight that these constituents vary in their alkyl chain length and in their linear or branching nature. Despite these structural differences, you consider that all the constituents of the substance can be regarded as "essentially linear".

72 You indicate that as a result in similarities in physicochemical properties, in molecular weight and in claimed similarity in metabolic pathways, among all the substances used in your weight of evidence adaptation, 1-tetradecanol (C14) linear would reflect a worst case for the prediction of long-term toxicity to aquatic invertebrates and that all constituents have similar properties (i.e. absence of effects) for the prediction of toxicity to algae.

73 All the lines of information used in your weight of evidence adaptation are derived from linear alcohols, other than that obtained from octadecanol branched for long-term toxicity to aquatic invertebrates. Some of these alcohols i.e. [redacted] are constituents of the Substance. The other lines of information are obtained from a linear alcohol (i.e. 1-tetradecanol, linear) of carbon chain length C14, which is shorter than the carbon chain length of the constituents of the Substance.

74 ECHA has assessed this information and identified the following issues:

75 The lines of information obtained from the constituents of the Substance provide information on the properties of these specific constituents to the extent of the investigations conducted in the corresponding lines of information, since these lines of information address the properties of constituents of the Substance. However, the available information on the constituent(s) of the Substance is not sufficient on its own to predict the properties of the Substance in that it does not address the contribution of the other constituents to the properties of the Substance.

76 The other lines of information are obtained from an analogue substance, i.e. 1-tetradecanol (C14) linear, and the following issues are identified for the prediction of the properties under consideration.

0.2.2.1.1. Regarding your hypothesis that all constituents have similar properties (i.e. absence of effects) for the prediction of toxicity to algae

77 You consider that the information from the analogue substance can be used to predict the properties of the constituents of the Substance based on similarities in their physico-chemical properties and molecular weights only. You do not provide information to support your claims associating the intrinsic physico-chemical properties of these analogue substances with similarities in ecotoxicological properties between this analogue substance and the constituents of the Substance.

78 Furthermore, while you consider that all the constituents of the Substance can be considered as "essentially linear", you have not provided information to support your assumption that the information on linear alcohols can be predictive of the properties of the branched constituents which are part of the composition of the Substance.

79 You do not provide information to support your claims associating intrinsic properties of the analogue substance with similarities in ecotoxicological properties of the Substance.

80 Therefore, you have not established that the analogue substance(s) can be used to reliably predict ecotoxicological properties of the Substance and you have not provided supporting information to strengthen the rationale for the read-across.

0.2.2.1.2. Regarding your hypothesis that 1-tetradecanol (C14) linear would reflect a worst case for the prediction of long-term toxicity to aquatic invertebrates

81 You consider that the information from the analogue substance can be used to predict the properties of the constituents of the Substance in a worst-case approach.

82 You provide the following two study summaries:

83 An expert statement claiming that "the C16, C18 and C20 constituents of the substance has been estimated by expert judgement to be non-toxic at the limit of solubility. You base this statement on indications "that no toxicity is observed at the limit of solubility with alcohols with carbon chain lengths ≥C15." In addition to this, you provide as an attachment the publication "Environmental properties of long-chain alcohols, Part 2: Structure–activity relationship for chronic aquatic toxicity of long-chain alcohols" by Schaefers et al. 2009.

84 Further, you provide a supporting study which you refer to as *Toxic Unit Approach* (PFA, 2013). In this study, you predict a NOEC for the Substance based on NOECs of its constituents taking into account their respective water solubilities. You conclude that "*The NOELR was estimated to be 0.17 mg/l, i.e. the NOEC for the toxic constituent would be reached at that nominal loading rate based on its dissolved concentration.*"

85 ECHA understands that you intend to use the above information to support your read-across approach for this endpoint and has assessed it in this regard.

86 Schaefers et al. 2009 provides information on long-term toxicity to daphnids with linear alkyl alcohols of the carbon chain lengths C10, C12, C14 and C15. The authors suggest a trend of increasing toxicity with increasing carbon chain lengths up to C14. The C15 alcohol is considered to have no long-term effects on aquatic invertebrates up to its solubility limit. In this study, no information on alkyl alcohols with C-chains ≥C16, linear or branched is provided. You did not explain how the provided data allows prediction of long-term toxicity to aquatic invertebrates for such substances, i.e. other constituents of the Substance. Therefore, this data cannot support your hypothesis that linear tetradecanol reflects the worst case among all constituents of the Substance.

87 PFA (2013) anticipates that none of the constituents of the Substance, but tetradecanol, linear exhibits long-term toxicity to aquatic invertebrates, because their NOEC would not be greater than their solubility limit in water. This statement does not provide any further data on the long-term toxicity to aquatic invertebrates with the Substance or its constituents that could confirm this assumption. Therefore, this information cannot be used to support your read-across.

88 In conclusion, you have not provided sufficient supporting information to strengthen the rationale for the read-across, i.e. that the information on the analogue substance(s) can be predictive of the properties of the branched or linear constituents of higher carbon chain lengths which are part of the composition of the Substance. You have not established that 1-tetradecanol, linear constitutes a worst-case for the prediction of the property under consideration of the Substance.

89 Moreover, while not considered reliable by you, the data you provide on octadecanol, branched, indicates that effects are observed for alkyl alcohol with carbon chain lengths of C18. Thus, it cannot reliably be ruled out that carbon chain lengths greater than C14 might induce long-term effects in daphnids.

90 Therefore, you have not established that the source substance(s) can be used to reliably predict ecotoxicological properties of the Substance and you have not provided supporting information to strengthen the rationale for the read-across.

Conclusion on the reliability of the information on the analogue substances

91 Based on the above, you have not established that the information on the analogue substance(s) of the Substance can reliably contribute to weight of evidence approaches intended to identify the properties of the Substance containing branched and linear constituents.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

92 An in vitro gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

1.1. Information provided

93 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) Bacterial reverse mutation assay according to the OECD TG 471 ([redacted] 1996) with the Substance;

(ii) Bacterial mutagenicity according to a method equivalent or similar to the OECD TG 471 ([redacted] 1980) with the substance dodecan-1-ol, EC 278-306-0.

94 You consider that the information that you have provided on the Substance itself and on the analogues substance, when taken together, is adequate to fulfil the information requirement under consideration.

1.2. Assessment of the information provided

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

96 As explained under Section 0.2 Reasons common to several requests, 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.

97 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.1 at Annex VII include:

- Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data provided on 5 bacterial strains: four strains of S. typhimurium (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

98 Study (i) provides information on some of these key elements only, i.e. using only 4 strains, i.e. S. typhimurium TA 1535, TA 1537, TA 98 and TA 100. This study is missing a strain which is capable of detecting oxidising mutagens, cross-linking agents and hydrazines.

99 Study (ii) provides information on all the key elements.

100 However, source of information (ii) has the following deficiencies affecting the reliability of its contribution to the weight of evidence approach:

1.2.1. Reliability of the contribution of the information on the analogue substance

101 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from study (ii) can reliably contribute to your weight of evidence adaptation.

1.2.2. Methodological deficiencies of experimental studies

102 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.

103 The source of information (ii) was conducted following the OECD TG 471. This test guideline requires that:

a) one positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.

104 In the source of information (ii), the following investigations/specifications are not to the requirements of OECD TG 471:

a) According to the information provided in your technical dossier, in multiple strains the positive control used in study (ii) did not produce the expected statistically significant increase in the number of revertant colonies per plate compared to the negative control and test item. This was particularly evident:

b) in experiment 3 for strains TA 98, TA 1538, TA 1537 and TA 100 in the absence of metabolic activation and TA 1537 in presence of metabolic activation.

c) in experiment 4 for the strain TA 100, TA 1538, TA 98 in absence of metabolic activation and TA 1537 in presence and absence of metabolic activation.

105 In the absence of a significantly positive response with the positive controls, the effective performance of the assay is not demonstrated and the results obtained from the study (ii) cannot be considered as reliable.

106 Based on the above, the reliability of the contribution of the results obtained from the study (ii) to the weight of evidence is limited.

1.2.3. Conclusion on the weight of evidence

107 Taken together, the only source of information that provides relevant information on all five strains of bacteria is source (ii). Source of information (i) does not provide information obtained in a strain capable of detecting oxidising mutagens, cross-linking agents and hydrazines.

108 However, the reliability of the contribution of the information obtained from source (ii) is hampered by:

- the deficiency identified related to the use of information on analogue substance and
- methodological deficiencies in the study design and/or reporting listed above affecting directly the reliability of the results of study (ii) and its contribution to the weight of evidence adaptation

1.3. Specification of the study design

109 To fulfil the information requirement for the Substance, the in vitro gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable and should be performed using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. Growth inhibition study aquatic plants

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

2.1. Information provided

111 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) a study on toxicity to algae with the source substance 1-tetradecanol, linear, EC 204-000-3
(ii) a study on toxicity to algae with the source substance 1-hexadecanol, linear, EC 253-149-0
(iii) a study on toxicity to algae on the source substance 1-octadecanol, linear, EC 204-017-6

You consider that the information that you have provided on the constituents of the Substance and the analogue substance, when taken together, is adequate to fulfil the information requirement under consideration.

2.2. Assessment of the information provided

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

Weight of evidence adaptation is rejected

113 As explained under section 0.2, 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.

114 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.2. at Annex VII includes similar information that is produced by OECD TG 201. This includes:

1) the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated.

115 While the sources of information (i), (ii) and (iii) provide relevant information on this key investigation, these sources of information have the following deficiencies affecting their reliability.

2.2.1. Reliability of the information on analogue substances

116 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (i) can reliably contribute to your weight of evidence adaptation.

2.2.2. Methodological deficiencies of experimental studies

117 In addition, ECHA has also identified the following endpoint specific issue with the reliability of the sources of information (i), conducted on analogue substance, and sources of information (ii) and (iii) conducted on constituents of the Substance.

118 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.

119 The sources of information (i), (ii) and (iii) were conducted following the OECD TG 201. This test guideline requires that:

120 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;
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.

121 Your registration dossier provides three studies (i), (ii) and (iii) showing the following:

122 Characterisation of exposure

a) no analytical monitoring of exposure was conducted without further justification;
b) you have expressed the effect values based on nominal concentrations. However, no data is provided demonstrating that exposure concentrations remained within ±20 % of the nominal or measured initial concentration throughout the test.

123 In section 1.4 of the CSR you provide the following water solubilities of the analogue substances: EC 204-000-3: 0.191 mg/L, EC 253-149-0: 0.024 mg/L, and EC 204-017-6: 0.001 mg/L. Therefore, based on the OECD GD 23 criteria the analogue substances are difficult to test due to the low water solubility.

124 No analytical monitoring of exposure concentrations was conducted and the effect values refer to nominal concentrations only. You did not provide data demonstrating that exposure concentrations remained within ±20 % of the nominal or measured initial concentration throughout the test. Therefore, ECHA cannot verify if the effect values reported are reliable.

125 Based on the above, the reliability of the contribution of the results obtained from the studies (i) to (iii) to the weight of evidence is limited.

2.2.3. Conclusion

126 Taken together, the sources of information as indicated above, provide relevant information on the toxicity to algae.

127 However, the reliability of the contribution of the information is hampered by:

- the use of information on analogue substance (study (i)) and
- methodological deficiencies in the study design and/or reporting listed above affecting directly the reliability of the results of studies (i), (ii) and (iii) and their contribution to the weight of evidence adaptation

128 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 TG 201. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2.3. Study design and test specifications

129 The Substance is difficult to test due to the low water solubility (<0.15 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. 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.

130 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).

131 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

132 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.

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).

133 In your dossier you report that the saturation concentration of the Substance in water was determined to be <0.15 mg/L.

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

135 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under request 10.

Reasons related to the information under Annex VIII of REACH

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

136 An in vitro cytogenicity study in mammalian cells or an in vitro micro-nucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

4.1. Information provided

137 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) *In vitro* chromosomal aberration test according to the OECD TG 473 ([redacted] 1998) with the substance tetradecan-1-ol, EC 267-019-6;

(ii) *In vitro* chromosomal aberration test according to the OECD TG 473 (Iglesias, 2002) with the substance docosan-1-ol, EC 211-546-6;

(iii) *In vivo* micronucleus study according to a test guideline equivalent or similar to the OECD TG 474 (Iglesias, 2002) with the substance docosan-1-ol, EC 211-546-6;

(iv) *In vivo* micronucleus study according to a test guideline equivalent or similar to the OECD TG 474 (Hachiya, 1982) with the substance octadecan-1-ol, EC 204-017-6;

(v) *In vivo* micronucleus study according to the OECD TG 474 ([redacted] 1992) with the substance dodecan-1-ol, EC 203-982-0.

138 You consider that the information that you have provided on the analogue substances, when taken together, is adequate to fulfil the information requirement under consideration.

4.2. Assessment of the information provided

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

140 As explained under Section 0.2 Reasons common to several requests, 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.

141 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2 at Annex VIII includes similar information that is produced by the OECD TGs 473/487. The OECD TGs 473/487 investigate the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

142 The sources of information (i) to (v) provide relevant information on the key elements listed above, but have the following deficiencies affecting the reliability of their contribution to the weight of evidence approach.

4.2.1. Reliability of the contribution of the information on the analogue substance (studies (i) to (iii) and (v))

143 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the studies (i) to (iii) and (v) can reliably contribute to your weight of evidence adaptation.

4.2.2. Methodological deficiencies of experimental studies (i) and (ii)

144 In addition, ECHA has also identified the following endpoint specific issue with the reliability of the information on analogue substances.

145 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.

146 Studies (i) and (ii) refer to in vitro chromosomal aberration tests performed according to the OECD TG 473. This test guideline requires that:

a) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 3 concentrations must be evaluated, in each test condition.
c) At least 300 well-spread metaphases must be scored per concentration.
d) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
e) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

147 In the studies (i) and (ii), the following investigations/specifications are not to the requirements of OECD TG 473:

a) A maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. No cytotoxicity and no precipitation was observed at the highest concentration of 20 µg/ml used in study (ii)
b) in study (i), only 1 concentration was tested with and without metabolic activation with a treatment time of 32h or treatment time of 3h and incubation time of 32h. In study (ii), only 1 test concentration was used in the experiment conducted with a fixation time of 7h.
c) in studies (i) and (ii) 100 cells were scored per replicate. Since the experiments were conducted in duplicate, only 200 cells were scored per concentration.
d) No positive control was used in the experiments of study (ii) with fixation times of 7h and 28h.
e) No details on the extent of the cytotoxicity observed in study (ii) are provided other than a reference to the concentration at which it is observed.

148 Based on the above, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited.

4.2.3. Conclusion

149 Taken together, the sources of information as indicated above, provide relevant information on the detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells.

150 However, the reliability of the contribution of the information is hampered by:

- the use of information on analogue substances (studies (i) to (iii) and (v)), and

- limitations of the study design and/or reporting listed above affecting directly the reliability of the results of studies (i) and (ii) and their contribution to the weight of evidence adaptation.

151 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 473/487. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

4.3. Specification of the study design

152 To fulfil the information requirement for the Substance, either 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) are considered suitable.

5. In vitro gene mutation study in mammalian cells

153 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.

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

155 The information for the in vitro gene mutation study in bacteria and for the in vitro cytogenicity study in mammalian cells or in vitro micronucleus study provided in the dossier are rejected for the reasons provided in sections 1 and 4.

156 The result of the requests for an in vitro gene mutation study in bacteria and for an in vitro cytogenicity study in mammalian cells will determine whether the present requirement for an in vitro mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

~~157~~ Consequently, you are required to provide information for this endpoint, if the in vitro gene mutation study in bacteria and the in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study provide a negative result.

5.1. Information provided

158 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) *In vitro* mammalian cell gene mutation test according to the OECD TG 476 (Iglesias, 2002) with the substance docosan-1-ol, EC 211-546-6;

(ii) Mammalian cell gene mutation assay according to a method equivalent or similar to the OECD TG 476 (Kirby, 1983) with the substance 2-ethyl hexan-1-ol, EC 203-234-3.

159 You consider that the information that you have provided on the analogues substances, when taken together, is adequate to fulfil the information requirement under consideration.

5.2. Assessment of the information provided

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

161 As explained under Section 0.2 Reasons common to several requests, 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.

162 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.

163 The sources of information (i) and (ii) 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.

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

164 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the studies (i) and (ii) can reliably contribute to your weight of evidence adaptation.

5.2.2. Methodological deficiencies of experimental studies (i) and (ii)

165 In addition, ECHA has also identified the following endpoint specific issue with the reliability of the information on analogue substances.

166 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.

167 Studies (i) and (ii) have been performed according to/test protocols similar to the OECD TG 476. This test guideline requires that:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.

b) One positive control must be included in the study. The study report must include information on the positive control substance used in the study.

168 In the sources of information (i) and (ii), the following investigations/specifications are not to the requirements of OECD TG 476:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. Specifically:

- No cytotoxicity and no precipitation was observed at the highest concentration of 20 µg/ml used in study (i) This suggests that the highest concentration used in study (i) is not the maximum concentration which can be tested.

- Furthermore, no information on the test doses used in study (ii) was provided in the endpoint study record included in your dossier. This prevents the assessment of the adequacy of the doses used in study (ii).

b) The endpoint study record for study (ii) indicates that a positive control has been used and that valid results were obtained. However, no information on the identity of the substance used as positive control is provided. In the absence of this information, the adequacy of the substance used as positive control cannot be assessed. Therefore, the effective performance of the assay is not demonstrated and the results obtained from the study (ii) cannot be considered as reliable.

169 Based on the above, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited.

5.2.3. Conclusion

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

171 However, the reliability of the contribution of the information is hampered by:

- the use of information on analogue substances (studies (i) and (ii)), and
- limitations of the study design and/or reporting listed above affecting directly the reliability of the results of studies (i) and (ii) and their contribution to the weight of evidence adaptation.

172 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. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

5.3. Specification of the study design

173 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. Screening for reproductive/developmental toxicity

174 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.

6.1. Information provided

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

(i) Combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD TG 422 ([redacted] 1992b) with the substance octadecan-1-ol, EC No. 204-017-6.

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

177 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.

6.2. Specification of the study design

178 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.

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

7. Long-term toxicity testing on fish

180 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.

181 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).

182 As already explained under request 2, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

183 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under request 11.

Reasons related to the information under Annex IX of REACH

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

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

8.1. Information provided

185 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) 28-day repeated dose toxicity according to the OECD TG 407 [redacted] 1986) with the substance octadecan-1-ol, EC 204-017-6;

(ii) Sub-chronic toxicity study, rats, oral route, no guideline followed ([redacted], 1966a) with the substance hexadecan-1-ol, EC 253-149-0;

(iii) Sub-chronic toxicity study, rats, oral route, no guideline followed ([redacted] 1966a) with the substance hexan-1-ol, EC 203-852-3.

186 You consider that the information that you have provided on the constituents of the Substance and the analogues substances, when taken together, is adequate to fulfil the information requirement under consideration.

8.2. Assessment of the information provided

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

188 As explained under Section 0.2 Reasons common to several requests, 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.

189 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2. at Annex IX includes similar information that is produced by the OECD TG 408. The following aspects of systemic toxicity are covered: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

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

8.2.1. Aspect 1) in-life observations

191 In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

192 The sources of information (i) to (iii) provide relevant information on aspect 1).

193 However, these sources of information have deficiencies affecting their reliability.

8.2.2. General reliability of the contribution of the information on analogue substances (study (iii))

194 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (iii) can reliably contribute to your weight of evidence adaptation.

8.2.3. Reliability of the contribution of the studies(i) to (iii) with regard to aspect 1)

195 Investigations/specifications in a sub-chronic toxicity study (OECD TG 408) include dosing of the Substance daily for a minimum of 90 days, i.e. 7 days a week over 13 weeks.

196 The study (i) has an exposure duration of 28 days only. The exposure period in studies (ii) and (iii) was 13 weeks, however, the animals were dosed only 5 days per week.

197 Based on the above, the actual exposure period in each of the studies (i) to (iii) is shorter than the minimum exposure duration expected from a study conducted according to the OECD TG 408. This condition of exposure is essential because the effects observed over the required period of exposure of 90-days might be considerably more pronounced than over a shorter study duration. Therefore, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited.

8.2.4. Aspect 2) blood chemistry

198 Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

199 The study (i) provides information on all the elements of aspect 2.

200 The studies (ii) and (iii) provide some relevant haematological information, although limited to a subset of the parameters listed in the OECD TG 408 i.e. they do not cover all the haematological information. The studies (ii) and (iii) do not provide relevant information on clinical biochemistry.

201 However, these sources of information have deficiencies affecting their reliability:

8.2.5. General reliability of the contribution of the information on analogue substances (study (iii))

202 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (iii) can reliably contribute to your weight of evidence adaptation.

8.2.6. Reliability of the contribution of the studies (i) to (iii) with regard to aspect 2)

203 The reliability issues identified in section 8.2.1.2 above, relating to exposure duration, and affecting studies (i) to (iii), equally apply to the aspect 2).

204 As a result, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited.

8.2.7. Aspect 3) organ and tissue toxicity

205 Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

206 The sources of information (i) to (iii) provide relevant information on some elements of aspect 3), but do not cover all the necessary information on gross pathology and full histopathology.

207 In particular, the information on gross pathology and full histopathology provided in the individual studies only covers a subset of the organs specified in the OECD TG 408. Specifically, the following organs were not investigated:

- In study (i): spinal cord, pituitary, parathyroid, oesophagus, salivary glands, stomach, small and large intestines, pancreas, trachea and lungs, aorta ovaries, uterus, cervix vagina, epididymides, prostate, seminal vesicle, coagulation glands, mammary glands, urinary bladder gall bladder, lymph nodes, peripheral nerves, skeletal muscle, bone, bone marrow;
- In studies (ii) and (iii): spinal cord, pituitary, thymus, oesophagus, salivary glands, trachea, aorta, uterus, cervix, vagina, prostate, coagulation glands, mammary gland, peripheral nerve, skeletal muscle

208 Furthermore, these sources of information have deficiencies affecting their reliability:

8.2.8. General reliability of the contribution of the information on analogue substances (study (iii))

209 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (iii) can reliably contribute to your weight of evidence adaptation.

8.2.9. Reliability of the contribution of the studies (i) to (iii) with regard to aspect 3)

210 The reliability issues identified in section 8.2.1.2 above, relating to exposure duration, and affecting studies (i) to (iii) equally apply to the aspect 3).

211 As a result, the reliability of the contribution of the results obtained from these studies to the weight of evidence is limited.

8.3. Conclusion on the weight of evidence

212 Taken together, the sources of information as indicated above, provide information on aspects 1 (in-life observations) and 2 (blood chemistry). However, for aspect 3 (organ and tissue toxicity), the sources of information provide relevant information only on some elements of this aspect, and do not cover the entire set of elements on gross pathology and full histopathology expected to be obtained from the OECD TG 408.

213 Furthermore, any robust conclusion on any of the 3 aspects is hampered by the same issues affecting all sources of information, i.e. use of information on analogue substances and too short exposure duration. These deficiencies increase the uncertainty of the results in such a way that prevents reaching a conclusion on any of these aspects.

214 Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study.

215 Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

8.4. Specification of the study design

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

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

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

9. Pre-natal developmental toxicity study in one species

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

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

(i) Combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test according to the OECD TG 422 ([redacted] 1992b) with the substance octadecan-1-ol, EC No. 204-017-6.

221 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.

222 In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation.

Source study not adequate for the information requirement

223 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case the OECD TG 414. Therefore, the following specifications must be met:

a) at least 20 female animals with implantation sites for each test and control;

b) examination of the foetuses for external, skeletal and soft tissue alterations (variations and malformations), measurement of anogenital distance in all live rodent foetuses.

224 In the study provided the following specifications are not according to the requirements of OECD TG 414:

a) 12 females are used in each dose and control group;

b) no data on examinations of skeletal and soft tissue alterations (variations and malformations) foetuses, no measurement of anogenital distance in all live rodent foetuses.

225 Based on the above, the study does not provide an adequate and reliable coverage of the key parameter(s) addressed by the OECD TG 414 and this study is not an adequate basis for your read-across predictions.

9.1. Specification of the study design

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

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

228 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

10. Long-term toxicity testing on aquatic invertebrates

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

10.1. Information provided

230 You have adapted this information requirement by using weight of evidence based on the following experimental data:

(i) an OECD 211 study with 1-tetradecanol, linear EC 204-000-3
(ii) a study similar to OECD 211 with 1-octadecanol, linear EC 204-017-6
(iii) a study according to EPA OPPTS 850.1300 (Daphnid Chronic Toxicity Test) with octadecanol, branched, EC No. not specified
(iv) a (Q)SAR prediction with 1-hexadecanol, linear EC 253-149-0

231 You consider that the information that you have provided on the constituents of the Substance and the analogue substance, when taken together, is adequate to fulfil the information requirement under consideration.

232 As regards to source of information (iii), you disregard this study due to major methodological deficiencies in your dossier and it is thus not taken into account for the assessment of the reliability of your weight of evidence.

10.2. Assessment of the information provided

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

234 As explained under section 0.2, 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.

235 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.5.at Annex IX includes similar information that is produced by OECD TG 211. This includes the following key investigations:

1. the reproductive output of *Daphnia sp.*, and
2. the survival of the parent animals during the test, and
3. the time to production of the first brood.

10.2.1. Concerning key investigation (1) the reproductive output of Daphnia sp.

236 The sources of information (i), (ii), (iii) and (iv) provide relevant information on this key investigation, but have the following deficiencies affecting their reliability.

10.2.1.1.1. Reliability of the information on analogue substances

237 For the reasons explained in the section 0.2 of the Reasons common to several requests above, you have not established that the information from the study (i) can reliably contribute to your weight of evidence adaptation.

10.2.1.1.2. Methodological deficiencies of experimental studies - source of information (ii)

238 In addition, ECHA has also identified the following endpoint specific issue with the reliability of the source of information (ii).

239 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.

240 The study of source of information (ii) was conducted following the OECD TG 211. This test guideline requires that:

241 Characterisation of exposure

a) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
b) if the concentration of the test material in semi-static tests, is not expected to remain within ± 20 % of the nominal concentration, then all test concentrations must be determined when freshly prepared and at the time of renewal on one occasion during each week of the test;

242 In your registration dossier, you provided study (ii) showing the following:

243 Characterisation of exposure

a) dissolved organic carbon (DOC) was used for analytical monitoring of exposure concentrations;
b) the test was conducted under semi-static conditions and the concentration of the test material was determined at 0, 48 and 120 hours;

244 In section 1.4 of the CSR you provide the following water solubility of the test material 1-octadecanol: 0.001 mg/L. Therefore, based on OECD GD 23 criteria 1-octadecanol is difficult to test due to the low water solubility.

245 DOC is not considered a substance specific or sensitive method for monitoring exposure concentrations and the sampling interval does not comply with the OECD TG 211 requirements. For the nominal test concentration of 10 mg/L, you report measured concentrations of 0.7, 1.15, 1.95 mg/L at 0, 48, 120 h, respectively, indicating a loss of the test material of more than 20 % compared to nominal concentration during the course of the study. Therefore, reported effect values based on nominal concentrations are considered not reliable.

246 Based on the above, the reliability of the contribution of the results obtained from the source of information (ii) to the weight of evidence is limited.

10.2.1.1.3. Reliability of the (Q)SAR prediction - source of information (iv)

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

(1) the prediction needs to be derived from a scientifically valid model,
(2) the substance must fall within the applicability domain of the model,
(3) results need to be adequate for the purpose of risk assessment or classification

and labelling, and

(4) adequate and reliable documentation of the method must be provided.

248 As regards condition (2), ECHA Guidance R.6.1.5.3. further specifies that a substance must fall within the applicability domain specified by the model developer.

249 In the QMRF provided you did not explicitly define the applicability domain of the model you used. ECHA understands that the applicability domain can be defined by the substances included in the training set which you report to be the following single carbon chain length alcohols:

- 1-octanol
- 1-decanol
- 1-dodecanol
- 1-tetradecanol
- 1-pentadecanol

250 In the QPRF to your (Q)SAR calculation you report that the model predicts long-term effects of alcohols to aquatic invertebrates in relation to logKow.

251 ECHA notes that the five substances used in the training set cover a logKow range of 3.2 to 6.4 and a carbon chain length range from C8 to C15.

252 Hexadecanol, linear has the following properties related to the estimation of that applicability domain: A logKow of 6.7 and a carbon chain length of C16.

253 Hexadecanol, linear does not fall in the applicability domain of the model, as its logKow and a carbon chain length are outside the training set.

254 The reported QSAR prediction does not fulfil the criteria in Annex XI, Section 1.3. Therefore, source of information (iv) is not reliable and cannot contribute to the conclusion on this key investigation.

10.2.2. Concerning key investigation (2) survival of parent animal during the test and key investigation (3) the time to produce the first brood

255 Source of information (iv) does not provide relevant information on these two key investigations, because it only indicates a NOELR based on reproduction but no information on parent animal survival or time of first brood.

256 The sources of information (i), (ii), and (iii), provide relevant information on these two key investigations. However, for the same reasons as already explained under section 10.2.1.1. above, the reliability of the sources of information (i) and (ii) is significantly affected. Therefore, these sources of information cannot contribute to the conclusion on these key investigations.

10.2.3. Conclusion

257 Taken together, the sources of information as indicated above, provide some relevant information on reproductive output of Daphnia sp., survival of parental animals and/or time of production of first brood.

258 However, the reliability of the contribution of the information is hampered by:

- the use of information on analogue substances (study (i)), and
- methodological deficiencies in the study design and/or reporting listed above affecting directly the reliability of the results of studies (ii) and their contribution to the weight of evidence adaptation, and

- the use of information from a QSAR prediction (study iv)

259 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 TG 211. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

10.3. Study design and test specifications

260 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' under request 3.

11. Long-term toxicity testing on fish

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

11.1. Information provided

262 You have provided the following information:

- the following justification to omit the study:
  "*According to REACH Annex XI, section 1, the studies required in Annex 9.1.6, are not needed for linear alcohols with carbon chains >C15 because sufficient information is available to predict no toxicity at their limit of solubility. Moreover, from experience gained in tests that have been conducted with substances in this category, considerable technical difficulties would be expected in the conduct of such a test, due to the very rapid biotic removal of the substance from the test system.*"
- in support to your adaptation you provide:
  (i) a study similar to EPA OTS 797.1000 (Fish Early-life Stage Toxicity Test) with pentadecanol, branched
  (ii) an expert statement on long-term toxicity to fish

11.2. Assessment of the information provided

263 While you refer to Annex XI section 1 in your justification, you did not specify which exact adaptation rule you intend to apply for omitting the study. However, as you have provided a study on an analogue substance, ECHA understands that you intend to adapt this information requirement under Annex XI Section 1.5 Grouping of substances and read-across.

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

Read-across adaptation rejected

265 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.

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

11.3. Study design and test specifications

267 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.).

268 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in ‘Study design’ under request 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 04 June 2021.

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

ECHA took into account your comments and amended the deadline.

Deadline to provide the information

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 32-34 months from the date of adoption of the decision. In order to support your request, you have provided a statement from a test laboratory detailing the different phases of the testing program covering the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), the sub-chronic toxicity study (OECD 408) and the pre-natal developmental toxicity study (OECD 414) requested in this decision. You indicate that according to the current approximate capacity of the laboratory, this testing program could be completed within 32-34 months while the remaining studies included in the draft decision can also be completed within this timeframe.

On this basis, ECHA has extended the deadline to 32 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[7].

1.2. Test material

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

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

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.