~~Confidential~~

Helsinki, 10 June 2022

Addressees
Registrant of [redacted] as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
09/01/2019

Registered substance subject to this decision ("the Substance")
Substance name: Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distilled
EC number: 700-991-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***15 September 2023***.

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

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

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

2. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

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.64/OECD TG 422) by oral route, in rats

An OECD TG 422 study (2005), is available in the jointly submitted registration for the Substance (Registration No. 01-2119502450-57-0000). Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the Substance.

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

8. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method: EU C.7./OECD TG 111)

9. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: EU C.18/OECD TG 106 or EU C.19/OECD TG 121)

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

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

An OECD TG 408 study (2019), is available in the jointly submitted registration for the Substance (Registration No. 01-2119502450-57-0000). Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the Substance.

11. 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)

An OECD TG 414 study (2019), is available in the jointly submitted registration for the Substance (Registration No. 01-2119502450-57-0000). Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the Substance.

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

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

14. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: EU C.13./OECD TG 305)

An OECD TG 305 study (2019), is available in the jointly submitted registration for the Substance (Registration No. 01-2119502450-57-0000). Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the Substance.

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 weight of evidence adaptations

1 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

2 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 Appendix, before assessing the specific standard information requirements in the following appendices.

3 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.

4 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.

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

6 You have not included a justification for your weight of evidence adaptation for each of the relevant information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

7 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.

0.1.1. Reliability of the provided information with analogue substances

8 ECHA understands that you intend to predict the toxicological properties of the Substance for the listed above endpoints, from data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation.

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

0.1.2. Unreliable studies (KL 4)

10 You have considered the sources of information as unreliable/unassignable, KL4:

i. Publication for the 90-day endpoint: Four Week Feeding Study of the test material in Sprague-Dawley Rats (1988) with test material: CAS#27193-86-8, no-GLP, under repeated dose toxicity endpoint.

ii. Publication for the gene mutation, screening and developmental toxicity endpoints: Letter From Monsanto Co To Usepa Regarding Toxicity Studies Of Dodecyl Phenol (1987) with test material: CAS#27193-86-2, not specified GLP, under genetic toxicity in vitro, toxicity to reproduction and developmental toxicity / teratogenicity endpoints.

11 ECHA agrees that these sources of information are unassignable/unreliable.

0.2. Assessment of the read-across approach

12 In your registration dossier you have provided information derived from experimental data from analogues using the OECD QSAR Toolbox and flagged the information as QSAR for the following standard information requirements:

- 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.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Adsorption/desorption screening (Annex VIII, Section 9.3.1.)

13 As the analogues are used as source substance(s) to predict the property of the Substance, we understand that you have adapted these standard information requirements under Annex XI, Section 1.5 of REACH (grouping and read-across).

14 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.

15 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.

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

17 We have assessed this information accordingly and identified the following issue[s]:

18 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.

19 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.

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

21 In your registration dossier you have formed groups (categories) for all endpoints covered by this section. The applicability domain of each category is defined by a number of referential and parametric boundaries listed in the reports attached in the respective sections of IUCLID registration dossier. The selection of category members was done by using OECD QSAR Toolbox and category members falling within applicability domain of respective category are listed in these reports.

22 The predictions of the properties for the Substance are based as follows:

- "*Takes average value from the 5 nearest neighbours*"

23 ECHA understands that this is the applicability domain of the grouping for respective properties and your predictions are assessed on this basis.

24 We have identified the following issue(s) with the proposed scope of the grouping:

0.2.1. Inadequate read-across hypothesis for categories build by OECD QSAR toolbox

25 A read-across hypothesis must be provided, establishing why a prediction for a (eco)toxicological or fate property is reliable. Firstly, this hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.). Secondly, it should explain why the differences in the chemical structures should not influence the (eco)toxicological/fate properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

26 Your read-across hypothesis is only based on the structural similarity between category members for categories build by OECD QSAR toolbox, which you consider a sufficient basis for predicting the properties of the Substance. However, your hypothesis does not explain why the structural differences between the substances do not influence the (eco)toxicological and fate properties or do so in a regular pattern.

27 While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar (eco)toxicological and fate properties. You have not provided a well-founded hypothesis to establish a reliable prediction for (eco)toxicological and fate properties, explaining why the structural differences do not influence the (eco)toxicological/fate properties or do so in a regular pattern, including toxicokinetics and toxicodynamics of the substances.

0.2.2. Missing robust study summaries

28 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 corresponding test method referred to in Article 13(3). In order to make an independent assessment of a key study, a robust study summary must be provided (Guidance on IRs and CSA, Section R.6.2.6; Art. 3(28) and 10(a)(vii) and Annex I, Section 1.1.4 and3.1.5 of REACH).

29 In your justification document you have identified the source substances, provided only the effect values for the respective property and did not provide anything on the study methods.

30 Therefore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the studies. In the absence of such information, the studies cannot be considered to provide an adequate and reliable coverage of the key parameters foreseen to be investigated in a study under to the corresponding OECD TG.

0.2.3. Prediction by OECD QSAR toolbox

31 The Guidance on IRs and CSA, Section R.6.2.2.1 explains that when applying quantitative read-across, there are four general ways of estimating the missing data point:

i. by using the endpoint value of a source chemical, e.g. the closest analogue in a (sub)category;
ii. by using an internal QSAR to scale the available experimental results from two or more source chemicals to the target chemical;
iii. by processing the endpoint values from two or more source chemicals (e.g. by averaging, by taking the most representative value);
iv. by taking the most conservative value of the closest analogues or the most conservative value in the (sub)category.

32 The documentation required by Annex XI, Section 1.5 must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[2]

33 As noted in the report provided in the registration dossier, prediction for all endpoints covered by this section is based on "*average value from the 5 nearest neighbours*".

34 However, it is not explained why the chosen approach of averaging effect values of nearest neighbours is applicable to predict specific property of the Substance from the category members.

35 Without such justification ECHA cannot conclude if the results of quantitative read-across are adequate for the purpose of classification and labelling and/or risk assessment and therefore, your quantitative estimation of adsorption coefficient is not acceptable.

0.2.4. Conclusion on the read-across approach

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

0.3. Triggering of long-term aquatic invertebrates and fish toxicity testing at Annexes VII and VIII

37 The same considerations provided below apply to the:

- Long-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1., column 2)
- Long-term toxicity testing on fish (Annex VIII, Section 9.1.3, column 2)

38 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

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.2.

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).

39 You have provided information which indicates that the Substance includes constituents that are poorly water soluble. More specifically, you identified the Substance to be UVCB with 5 constituents, including one identified as 'sum of unknown constituents', and provided non-standard water solubility study (by HPLC method) where the total saturation concentration of the Substance in water was determined to be 1.4 mg/L at 25 °C, i.e. only one constituent can have a water solubility above 1 mg/L, therefore other constituents have water solubility below 1 mg/L.

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

0.4. Assessment of (Q)SAR information

41 You seek to adapt the following standard information requirements by applying (a) (Q)SAR approach(es) in accordance with Annex XI, Section 1.3:

- Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.)

42 To support the adaptation, you have provided following information:

- prediction of Hydrolysis as a function of pH by "*AOPWIN programme of EPI suite*";
- predictions of long-term toxicity testing to fish and aquatic invertebrates by ECOSAR version 1.11;
- key study: prediction of BCF (bioconcentration factor) by BCFBAF version 3.01.

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

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

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

45 With regard to these conditions, we have identified the following issues:

0.4.1. Lack of documentation of the prediction (QPRF)

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

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,

- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

47 You have not provided any information about the predictions of Hydrolysis as a function of pH, bioaccumulation and long-term toxicity to fish and aquatic invertebrates including on how single (no-)effect concentration for each, fish and aquatic invertebrates and single BCF, were estimated for the UVCB substance containing multiple constituents.

48 In absence of such information, ECHA cannot establish that the prediction can be used to meet these information requirements.

0.4.2. Adequacy of predictions for bioaccumulation

49 Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

50 All the structures selected for prediction must fulfil the above conditions.

51 Your registration dossier provides the following information:

- log Kow (or log Pow) of constituents of the Substance >4 (OECD TG 117)
- in respect of BCF by BCFBAF v3.01 that "*Result based on measured log Pow of: 8.72*"

52 The origin of the inputted single log Kow (or of log Pow as referred by you in the registration dossier) of 8.72 is unknown and therefore, reliability of this parameter cannot be confirmed. Consequently, you have not demonstrated that the prediction of BCF for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

0.4.3. Modelled endpoint by AOPWIN

53 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in the case of hydrolysis as a function of pH includes (i) the rate of hydrolysis of the test substance as a function of pH and (ii) the identity or nature and rates of formation and decline of hydrolysis products (OECD TG 111).

54 ECHA Guidance R.7b (Table R.7.9-1) defines that hydrolysis is "Decomposition or degradation of a substance by reaction with water".

55 You specify that the effect ("hydrolysis rate constant of test chemical") was estimated by "AOPWIN programme of EPI suite". In the Introduction of User Guide of AOPWIN (v1.92) it is explained that "The Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) estimates the rate constant for the atmospheric, gas-phase reaction between

photochemically produced hydroxyl radicals and organic chemicals. It also estimates the rate constant for the gas-phase reaction between ozone and olefinic/acetylenic compounds. The rate constants estimated by the program are then used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radicals and ozone.". Thus, the AOPWIN does not predict neither of the effects measured by the OECD TG 111.

56 Therefore, the endpoint(s) of the model is not what is measured by the relevant information requirement test protocol, i.e. OECD TG 111.

57 Based on the above, your adaptations are rejected.

0.5. Data sharing issues

58 The jointly submitted registration for the Substance contains data which is relevant for the following requests: 1, 2, 4, 5, 8, 9, 12. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

59 The jointly submitted registration for the Substance contains data which is relevant for the following requests 6, 10, 11, 14. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[1].

[1] https://echa.europa.eu/regulations/reach/registration/data-sharing

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

60 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

61 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

62 You have provided the following sources of information to support your adaptations:

i. QSAR, Estimation for Gene mutation for mixture with Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distilled)

ii. Publication: Letter From Monsanto Co To Usepa Regarding Toxicity Studies Of Dodecyl Phenol, With Attachments And Dated 5/22/96 (1987), with a constituent (CAS#27193-86-2)

iii. Publication: Mutagenic, carcinogenic and cocarcinogenic activity of cashewnut shell liquid (1996), with the Substance

1.2. Assessment of the information provided

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

1.2.1. Missing documentation of the weight of evidence

64 As explained in Section 0.1. of the Appendix Reasons common to several requests, the weight of evidence must fulfill 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.

65 As explained in Section 0.1. of the Appendix Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

66 The key parameter investigated by OECD TG 471 test is detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies.

67 All the studies investigate partly the above mentioned key parameter. Therefore, they are relevant and provide information that would contribute to the conclusion on this key parameter.

68 However, the reliability of the sources of information is significantly affected.

1.2.2. Weight of Evidence: Significant reliability issues

69 The reliability of the sources of information is significantly affected by the deficiencies identified in Section 0.1 of the Appendix on Reasons common to several requests.

70 In addition, the reliability of the sources of information is also affected by the following issues.

71 Under OECD TG 471 (2020), the following specifications must be met:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 µl/plate.

c) At least 5 doses must be evaluated, in each test condition.

d) 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.

e) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

72 The study (iii.) is described as "in vitro gene mutation study in bacteria". However, the following is missing:

a) results for the appropriate 5 strains, that is in TA98/TA100/TA1535/TA1537 or TA97a or TA97/the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

b) a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance.

c) the evaluation of at least 5 doses in each test condition.

d) a positive control.

e) data on the number of revertant colonies per plate for the treated doses and the controls.

73 The reliability of this study is therefore significantly affected.

74 Taken together, even if the sources of information (i-iii) may provide some information on the key parameter, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

75 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 property foreseen to be investigated by the required study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

1.2.3. Read-across adaptation rejected

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

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

1.3. Specification of the study design

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

1.4. Information regarding data sharing

79 Information on data sharing obligations are addressed under Section 0.5.

2. Long-term toxicity testing on aquatic invertebrates

80 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. As already explained under Section 0.3 above, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

81 On this basis, the information requirement is triggered.

2.1. Information provided

82 You have provided an adaptation by applying a weight of evidence (WoE) in accordance with Annex XI, section 1.2 for the short-term toxicity testing on aquatic invertebrates, but no information on long-term toxicity on aquatic invertebrates for the Substance.

2.2. Assessment of the information provided

83 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under this Appendix, Section 12 below.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

85 You have provided a study according to OECD TG 201 (2015, no GLP compliance).

3.2. Assessment of the information provided

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

3.2.1. The provided study does not meet the information requirement

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

- Key parameter to be measured: 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. growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period;

- Validity criterion: the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;
- three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;
- the concentrations of the test material are measured at least at the beginning and end of the test:
    i. at the highest, and
    ii. at the lowest test concentration, and
    iii. at a concentration around the expected EC_{50}.

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

- the concentration of the test material leading to a 50 % inhibition of growth at the end of the test is estimated; growth is expressed on the basis of cell number;
- the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is app. 50%;
- two replicates at each test concentration were used;
- stock solution concentration at the beginning of the test was analytically verified, but no analytical monitoring of the concentrations of the test material at the end of the test was conducted.

89 Based on the above,

- the key parameter of OECD TG 201 is not covered: the concentration of the test material leading to a 0% (or 10%) inhibition of growth at the end of the test is not estimated; growth is not expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period;
- the validity criterion of OECD TG 201 noted above is not met;
- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically only two replicates at each test concentration were used (while at least three replicates must be used when the concentration of the test material leading to a 0% (or 10%) inhibition of growth at the end of the test is estimated) and the concentrations of the test material throughout the test duration were not analytically verified (monitored).

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

3.2.2. Compliance with principles of good laboratory practice

91 Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

92 You indicate in the registration dossier that provided study was performed in 2015 and was not performed according to GLP.

93 Thus, the study does not comply with requirements of Article 13(4) of REACH.

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

3.3. Study design and test specifications

95 The Substance is difficult to test due to the low water solubility of the constituents of the Substance (as already explained in Section 0.3 above) and adsorptive properties of the constituents of the Substance (log Kow >4). 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.

96 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).

97 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.

Reasons related to the information under Annex VIII of REACH

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

98 An in vitro cytogenicity study in mammalian cells or an in vitro micronucleus study is a standard information requirement in Annex VIII to REACH.

4.1. Information provided

99 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

100 You have provided the following source of information to support your adaptations:

i. QSAR: Estimation for Chromosome aberration for mixture (2015)

101 In addition, you have provided one in vivo study:

ii. Publication: Evaluation of the toxic, cytotoxic, mutagenic and antimutagenic effects of natural and technical cashew (Anacardium occidentale L.) nut shell liquid on root meristems of *Allium cepa* using Artemia salina bioassay (2015)

4.2. Assessment of the information provided

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

4.2.1. Missing documentation of the weight of evidence

103 As explained in Section 0.1 of the Appendix Reasons common to several requests, the weight of evidence adaptation must fulfill 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.

104 As explained in Section 0.1. of the Appendix on Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

105 For this endpoint your study needs to have adequate and reliable coverage of the key parameters foreseen to be investigated in an OECD TG 473 or 487 test. The key parameter investigated by these tests is 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.

106 The source of information (i) provides some relevant information on chromosomal aberrations in cultured mammalian cells.

107 You describe information source (ii) as a in vivo mammalian germ cell study: cytogenicity / chromosome aberration. However, the test species is Allium cepa and plant chromosomal aberrations data is not comparable to in vivo mammalian studies.

108 Therefore, only source (i) provides relevant information. However, the reliability of the source of information (i) is significantly affected by the deficiencies identified in Section 0.1 of the Appendix on Reasons common to several requests.

109 Taken together, even if the source of information (i) may provide some information on the key parameter, its reliability is affected so significantly that it cannot be taken into consideration in a weight of evidence approach. The source of information (ii) does not provide relevant information on chromosomal aberrations comparable to in vivo mammalian studies.

110 Therefore, it is not possible to conclude whether your Substance has or has not the particular dangerous property foreseen to be investigated by the required study.

111 Therefore, your adaptation according to Annex XI, Section 1.2 is rejected and the information requirement is not fulfilled.

4.2.2. Read-across adaptation rejected

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

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

4.3. Specification of the study design

114 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.

4.4. Information regarding data sharing

115 Information on data sharing obligations are addressed under Section 0.5.

5. In vitro gene mutation study in mammalian cells

116 An in vitro gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

117 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.

118 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.

119 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.

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

5.1. Information provided

121 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

122 You have provided the following sources of information to support your adaptations:

i. Publication: In vitro antiproliferative/cytotoxic activity on cancer cell lines of a cardanol and a cardol enriched from Thai Apis mellifera propolis (2015).

123 In addition, you have provided one in vivo study:

ii. Publication: Evaluation of the toxic, cytotoxic, mutagenic and antimutagenic effects of natural and technical cashew (Anacardium occidentale L.) nut shell liquid on root meristems of *Allium cepa* using Artemia salina bioassay (2015).

5.2. Assessment of the information provided

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

5.2.1. Missing documentation of the weight of evidence

125 As explained in Section 0.1 of the Appendix Reasons common to several requests, the weight of evidence adaptation must fulfill 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.

126 As explained in Section 0.1. of the Appendix Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

127 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 TG 476/490 and OECD TG 488. This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (in vivo).

128 You describe information source (i) as a publication of mammalian cell gene mutation assay without further details on conducted studies. This does not qualify as adequate documentation. Furthermore, the data provided does not address gene mutation but antiproliferative/cytotoxic activity on cancer cell lines. Therefore it is not relevant to the endpoint.

129 You describe information source (ii) as an in vivo mammalian germ cell study: gene mutation. However, the test species is Allium cepa and plant gene mutation data is not comparable to in vivo mammalian studies.

130 Therefore, none of the sources provide relevant information.

131 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 vitro gene mutation study in mammalian cells.

132 Therefore your adaptation according to Annex XI, Section 1.2 is rejected and the information requirement is not fulfilled.

5.2.2. Read-across adaptation rejected

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

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

5.3. Specification of the study design

135 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.

5.4. Information regarding data sharing

136 Information on data sharing obligations are addressed under Section 0.5.

6. Screening for reproductive/developmental toxicity

137 A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or in vitro methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

6.1. Information provided

138 A screening for reproductive/developmental toxicity (OECD 421 or OECD 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII to REACH or a general adaptation rule under Annex XI to REACH.

139 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

140 You have provided the following sources of information to support your adaptations:

i. Predicted data from QSAR toolbox 3.1 (2014) for read-across predictions with CAS 96-69-5, 119-47-1, 125643-61-0, 79-94-7, 110553-27-0.

ii. Publication: Letter From Monsanto Co To Usepa Regarding Toxicity Studies Of Dodecyl Phenol (1987) with test material: CAS#27193-86-2, not specified GLP.

iii. Publication: Studies on the reproductive, cytological and biochemical toxicity of Ginkgo Biloba in Swiss albino mice (2006) with test material: CAS#8007-24-7, not specified GLP.

6.2. Assessment of the information provided

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

6.2.1. Missing documentation of the weight of evidence

142 As explained in Section 0.1 of the Appendix Reasons common to several requests, the weight of evidence adaptation must fulfill 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.

143 As explained in Section 0.1. of the Appendix Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

6.2.2. Study not relevant and/or not conducted using a recognised test method

144 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

6.2.2.1. Sexual function and fertility

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

146 The source of information (iii.) provide limited information on sexual function and fertility. More specifically, they provide information only on male reproductive organs and male parameters and mating. Presumed gestation is terminated at 13 days following the mid-week of their presumptive mating and there are no observations and examinations performed to females, except rate of pregnancy and mean implants per female. Information is missing on maintenance of pregnancy, parturition, lactation, organ weights and histopathology of reproductive organs and tissues of females and nursing performance.

147 The sources of information (i.) and (ii.) do not provide any relevant information.

148 The reliability of thee source of information iii. is significantly affected by the deficiencies identified in Section 0.1 of the Appendix on Reasons common to several requests.

6.2.2.2. Toxicity to offspring

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

150 No source of information provides information on toxicity to offspring. Information on offspring parameters in source of information (iii), in particular, is lacking as the presumed pregnant females were terminated in early phase of presumed pregnancy. There were no examination of fetal development or pups born.

6.2.2.3. Systemic toxicity

151 Information on systemic toxicity include information on clinical signs with specific observations, survival, body weights, food consumption, haematology, clinical

biochemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

152 No source of information provides any information on systemic toxicity.

153 Therefore, there is lack of information on aspects of systemic toxicity foreseen to be investigated in an EU B.63/OECD TG 421.

154 Taken together, the sources of information, as indicated above, provide some information on reproductive toxicity but essential parts of information of the hazardous property is lacking, including information on: mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility; and toxicity to offspring and systemic toxicity.

155 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 EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

6.2.3. Read-across adaptation rejected

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

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

6.3. Specification of the study design

158 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.

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

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

6.4. Information regarding data sharing

161 Information on data sharing obligations are addressed under Section 0.5.

7. Long-term toxicity testing on fish

162 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. As already explained under Section 0.3 above, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

7.1. Information provided

163 You have provided an OECD TG 203 study, but no information on long-term toxicity on fish for the Substance.

7.2. Assessment of the information provided

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

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

166 The examination of the information provided, as well as the selection of the requested test and the test design are addressed under this Appendix, Section 13 below.

8. Hydrolysis as a function of pH

167 Hydrolysis as a function of pH is an information requirement under Column 1 of Annex VIII to REACH (Section 9.2.2.1.).

8.1. Information provided

168 You have provided an adaptation in accordance with Annex XI, section 1.3 ((Q)SAR). To support the adaptation, you have provided prediction by "AOPWIN programme of EPI suite".

8.2. Assessment of the information provided

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

170 As already explained under Section 0.4 above, your adaptation is rejected.

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

9. Adsorption/ desorption screening

172 Adsorption/desorption screening is an information requirement under Column 1 of Annex VIII to REACH (Section 9.3.1.).

9.1. Information provided

173 You have provided an adaptation in accordance with Annex XI, section 1.5 (grouping and read-across). To support the adaptation, you have provided information derived from experimental data from analogues using the OECD QSAR Toolbox.

9.2. Assessment of the information provided

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

175 As already explained under Section 0.2 above, your adaptation is rejected.

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

Reasons related to the information under Annex IX of REACH

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

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

10.1. Information provided

178 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

179 You have provided the following sources of information to support your adaptations:

(i) Predicted data from QSAR toolbox 3.1 (2014) for read-across predictions with CAS 96-69-5, 119-47-1, 125643-61-0, 79-94-7, 110553-27-0.

(ii) Publication: Four Week Feeding Study of the test material in Sprague-Dawley Rats (1988), with 2-dodecylphenol EC#248-312-8, no-GLP,

(iii) Publication: Chronic Administration of Cardanol (Ginkgol) Extracted from Ginkgo biloba Leaves and Cashew Nutshell Liquid Improves Working Memory-Related Learning in Rats (2012), with the Substance as a constituent.

10.2. Assessment of the information provided

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

10.2.1. Missing documentation of the weight of evidence

181 As explained in Section 0.1 of the Appendix Reasons common to several requests, the weight of evidence adaptation must fulfill 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.

182 As explained in Section 0.1. of the Appendix Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI, Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

10.2.2. Source studies not adequate and/or not reliable for the information requirement

183 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system. This information is covered by information similar to OECD TG 408.

10.2.2.1. In-life observations

184 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).

185 Source of information (iii.) provide relevant information on survival, body weight clinical signs, food/water consumption and neurobehavioural examination (Memory-Related Learning ability). However, any other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, renal/urinary, and respiratory) was not reported. Therefore, these sources of information provides limited information on this key element.

186 Sources of information (i) and (ii) do not provide relevant information.

187 While the source of information (iii.) provide partly relevant information on survival, body weight clinical signs, food/water consumption and memory-related Learning ability, this source of information has the following deficiency affecting its reliability.

188 The conditions of exposure in accordance with the OECD TG 408 specifies that dosing of the Substance is performed daily for a period of 90 days until the scheduled termination of the study. Furthermore, at least three dose levels and a concurrent control shall be used, and both female and male animals should be used at each dose level.

189 However, source of information (iii.) has an exposure duration of 60 days. Furthermore, only one dose group was included with only male animals tested.

190 Therefore, source of information (iii.) has significant reliability issues.

10.2.2.2. Blood chemistry

191 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)

192 No source of information provides information on blood chemistry.

10.2.2.3. Organ and tissue toxicity

193 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).

194 No source of information provides information on organ and tissue toxicity.

10.2.2.4. Conclusion on weight of evidence

195 Therefore, there is lack of information on several aspects of sub-chronic toxicity foreseen to be investigated in an OECD TG 408. As indicated above, the source of information (iii.) provide partly relevant information on in-life observations, but its reliability is significantly affected. There is no relevant information on blood chemistry or organ tissue toxicity.

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

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

10.2.2.5. Read-across adaptation rejected

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

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

10.3. Specification of the study design

200 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.

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

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

10.4. Information regarding data sharing

203 Information on data sharing obligations are addressed under Section 0.5.

11. Pre-natal developmental toxicity study in one species

204 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.).

11.1. Information provided

205 You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2 of REACH and a read-across adaptation under Annex XI, Section 1.5 of REACH.

206 You have provided the following sources of information to support your adaptations:

(i) Predicted data from QSAR toolbox 3.1 (2014) for read-across predictions with CAS 96-69-5, 119-47-1, 125643-61-0, 79-94-7, 110553-27-0.

(ii) Publication: Letter From Monsanto Co To Usepa Regarding Toxicity Studies Of Dodecyl Phenol, With Attachments And Dated 5/22/96 (1987), not specified GLP with test material 2-docecylphenol EC#248-312-8.

(iii) Publication: Studies on the reproductive, cytological and biochemical toxicity of Ginkgo Biloba in Swiss albino mice (2006), not specified GLP, RL2, with CAS#8007-24-7.

11.2. Assessment of the information provided

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

11.2.1. Missing documentation of the weight of evidence

208 As explained in Section 0.1 of the Appendix Reasons common to several requests, the weight of evidence adaptation must fulfill 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.

209 As explained in Section 0.1. of the Appendix Reasons common to several requests, your documentation of the weight of evidence is not in line with the requirements of Annex XI,

Section 1.2. Therefore, your adaptation is rejected. In addition, ECHA identified endpoint-specific issue(s) regarding the weight of evidence. These are addressed below.

11.2.2. Source studies not adequate and/or not reliable for the information requirement

210 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

11.2.2.1. Pre-natal developmental toxicity

211 Pre-natal developmental toxicity includes information after pre-natal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

212 The sources of information do not provide any relevant information on embryonic/foetal survival, growth and structural malformations and variations.

213 Taken together, the information on prenatal developmental toxicity provided is not relevant.

11.2.2.2. Maternal toxicity

214 Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

215 The sources of information do not provide information on maternal toxicity. Females were necropsied 13 days following the mid-week of their caging and presumptive mating and only parental animals were examined.

216 The sources of information do not provide relevant information.

11.2.2.3. Maintenance of pregnancy

217 Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

218 The sources of information (iii) provide limited information on maintenance of pregnancy as females were necropsied 13 days following the mid-week of their caging and presumptive mating.

219 The other sources of in formation do not provide relevant information.

220 Taken together, the sources of information provide very limited relevant information on maintenance of pregnancy and the relevant information is not reliable. However, the provided sources of information do not provide relevant information on prenatal developmental toxicity or maternal toxicity.

11.2.3. Conclusion on weight of evidence

221 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 OECD TG 414. Therefore, your adaptation is rejected.

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

11.2.4. Read-across adaptation rejected

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

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

11.3. Specification of the study design

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

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

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

11.4. Information regarding data sharing

228 Information on data sharing obligations are addressed under Section 0.5.

12. 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.).

12.1. Information provided

230 You have provided the following information:

- an adaptation under Annex XI, Section 1.3. ((Q)SAR). In support of your adaptation, you provide the following information: a prediction derived from ECOSAR version 1.11.

12.2. Assessment of the information provided

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

232 As already explained under Section 0.4 above, your adaptation is rejected.

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

12.3. Study design and test specifications

234 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 Section 3.3 above.

13. Long-term toxicity testing on fish

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

13.1. Information provided

236 You have provided the following information:

- an adaptation under Annex XI, Section 1.3. ((Q)SAR). In support of your adaptation, you provide the following information: a prediction derived from ECOSAR version 1.11.

13.2. Assessment of the information provided

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

238 As already explained under Section 0.4 above, your adaptation is rejected.

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

13.3. Study design and test specifications

240 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.).

241 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 Section 3.3 above.

14. Bioaccumulation in aquatic species

242 Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

14.1. Information provided

243 You have provided the following information:

- key study: an adaptation under Annex XI, Section 1.3. (Q)SAR); in support of your adaptation, you provide the following information: a prediction derived from BCFBAF version 3.01.
- supporting study: an adaptation under Annex XI, Section 1.5. (grouping and read-across); in support of your adaptation, you provide the following information: information on the experimental BCF "*from J-CHECK authoritative database*" for analogous substance 2-dodecylphenol (EC No 248-312-8).

14.2. Assessment of the information provided

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

14.2.1. Rejection of adaptation under Annex XI, Section 1.3.

245 As already explained under Section 0.4 above, your adaptation is rejected.

14.2.2. Assessment of adaptation under Annex XI, Section 1.5.

246 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.

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

248 You predict the properties of the Substance from information obtained from the source substance: 2-dodecylphenol (EC No 248-312-8).

249 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

14.2.2.1. Absence of read-across documentation

250 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the study(ies) on the source substance(s) (Guidance on IRs and CSA, Section R.6.2.6.1.).

251 You have provided a study summary for a study conducted with other substance than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance.

252 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance.

14.2.2.2. Adequacy and reliability of study on the source substance

253 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 corresponding test method referred to in Article 13(3). In order to make an independent assessment of a key study, a robust study summary must be provided (Guidance on IRs and CSA, Section R.6.2.6; Art. 3(28) and 10(a)(vii) and Annex I, Section 1.1.4 and 3.1.5 of REACH).

254 Robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

255 In your justification document you have identified the source study as supporting study but provided only: the BCF value, route of exposure – aqueous, total duration (60 days), lipid content at start of exposure, identity of test organisms (Cyprinus carpio) and aqueous concentration (0.001 mg/l).

256 Therefore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the study. In the absence of such information, the study cannot be considered to provide an adequate and reliable coverage of the key parameters foreseen to be investigated in a study under to the corresponding OECD TG.

14.2.2.3. Conclusion on the read-across approach

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

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

14.3. Study design and test specifications

259 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

260 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

261 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

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 05 November 2020.

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

ECHA did not receive any comments within the commenting period.

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]

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[3].

1.2. Test material

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

   The Test Material used to generate the new data must be selected taking into account the following:

   a) the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. *Information on the Test Material needed in the updated dossier*

   a) You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals