~~Confidential~~

Helsinki, 10 June 2022

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

Date of submission of the dossier subject to this decision
23/09/2021

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 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. 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

2. 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

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

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

4. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit)

5. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
   - Cohorts 2A and 2B (Developmental neurotoxicity); and

- Investigations on learning and memory function as described in paragraph 37 of the OECD TG 426.

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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

[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.

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Appendix 1: Reasons for the decision

Contents

Reasons related to the information under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

1.1. Information provided

2 You have provided the following information:

- an adaptation under Annex XI, Section 1.5. ('Grouping of substances and read-across').
- In support of your adaptation, you provide the following information:
  (i) a study according to ISO 10253 on the analogue substance Cashew (*Anacardium occidentale*) Nutshell Extract, Decarboxylated with EC List No. 941-216-3.

1.2. Assessment of the information provided

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

4 You provide "endpoint level" justification in the IUCLID registration dossier, Section 6.1.5. Furthermore, you note that "Further details on the justification for using the interpolation based read-across approach are given in the attached document" (justification document is provided in IUCLID Section 13).

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

1. Distilled Grade Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distilled, EC No. 700-991-6. (the Substance)
2. Technical Grade Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, EC List No. 941-216-3.
3. Distillation Residue Grade Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distillation Residue, EC List No. 941-212-1.

6 In the read-across justification document provided in IUCLID Section 13 you justify the grouping of the substances as:

7 "Analysis of the three grades of processed cashew nutshell extract indicates that they all contain the same five key constituent groups [..]. In terms of the balance between the lower molecular weight non-polymeric constituents (such as [redacted]) and the higher molecular weight polymeric constituents Technical Grade compositionally lies between Distilled and Distillation Residue Grades. […] available physico-chemical, environmental fate and pathways, mammalian toxicity and ecotoxicity data […] for the three grades of processed Cashew Nutshell Extract show that: 1.They represent a group or category based on structural and compositional similarities. 2.An interpolation approach can be applied whereby data for the source substances of the category (Distilled and Distillation Residue Grades) can be used to generate data for the target substance Technical Grade.".

8 On the basis of the above, ECHA understands that you define the structural basis for the grouping as: "category/grouping approach for the three grades of processed Cashew Nutshell Extract with read-across of data for the target substance Technical Grade by interpolation from the source substances Distilled and Distillation Residue Grades".

9 ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

10 You predict toxicity of aquatic plants of the Substance from information obtained from the following source substance: Technical Grade.

11 You provide the following reasoning for the prediction of the short-term aquatic toxicity properties in the IUCLID registration dossier, Section 6.1.5: "The available data for the three grades indicates that they all show low measured water solubility in the range 0.2 to 0.3 mg/l. All three substances also show high measured octanol-water partition coefficients (log Kow >6.2 in all cases). This data indicates that the measured data for the key physico-chemical properties that underpin the likely short term aquatic toxicity of the three grades are consistent. On this basis it would be expected that the three grades would show similar responses in the short-term aquatic toxicity tests. This hypothesis is currently supported by the results of the results of the long-term OECD TG 218 ecotoxicity test that was conducted on both Distilled Grade and Distillation Residue grade following the interpolation approach. Therefore, it is considered appropriate to read-across from the data for Technical Grade to Distilled Grade with the result that it has been estimated that there will also be no adverse toxicological effects of Distilled Grade on algal growth at the substances water solubility limit."

12 In your comments to the draft decision you note that "there appears to be a misinterpretation of the approach being taken" and since similar results, i.e. no adverse effects, were observed in OECD TGs 218 and 211 studies carried out on Distilled and Distillation Residue Grades "similar outcomes are expected for these tests on Technical Grade". Furthermore, you note that "the absence of responses in the long-term tests are consistent with the low levels of bioaccumulation of the key non-polymeric constituents of both Distilled and Distillation Residue grades […] is being explored to strengthen the rationale for the read-across" and "that the constituents of the substances capable of causing either acute and/or long-term toxicity to aquatic species do not reach the internal levels required to cause adverse effects". You note that in contrast "the data for the repeated dose mammalian toxicity endpoints (from the OECD TG408 and TG414 tests) evidently shows that Distilled Grade exerts greater toxicity than Distillation Residue Grade. However, the data still follows a regular pattern in accordance with RAAF Scenario 4, meaning that the interpolated responses of Technical Grade are predictable". You note that "it should be recognised that this approach has been agreed with the Agency in the Final Decisions for the Annex IX and X testing of Distilled (TPE-D-2114350280-62-01/F) and Distillation Residue (TPE-D-2114350287-48-01/F) Grades from March 2018."

13 ECHA understands that your read-across hypothesis for the short-term aquatic toxicity properties 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.

1.2.1. Read-across hypothesis contradicted by existing data

14 Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances". The Guidance on IRs and CSA, Section R.6.2.2.1.f. indicates that "it is important to provide supporting information to strengthen the rationale for the read-across". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance.

15 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why

such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

16 Your read-across hypothesis provided in the IUCLID registration dossier, Section 6.1.5 is "that the three grades would show similar responses in the short-term aquatic toxicity tests".

17 In the "endpoint level" justification provided in the IUCLID registration dossier, Section 6.1.5 you indicate that Distilled Grade "was considered to be the most (eco) toxicologically active form, given the higher content of low molecular weight constituents (such as cardanol) and the low content of polymeric species".

18 Furthermore, in the read-across justification document in IUCLID Section 13 you note that:

- "*An interpolation approach can be applied whereby data for the source substances of the category (Distilled and Distillation Residue Grades) can be used to generate data for the target substance Technical Grade.*"
- "In both the mammalian toxicity studies (OECD TG408 and TG414) different results with regard to systemic toxicity were obtained for the source substances". *In both instances the tests on Distilled Grade showed greater toxicity (in terms of lower No Observed Adverse Effect Levels) than those conducted on Distillation Residue Grade.*"

19 The available set of data on the Substance and on the source substances indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substance cause the same type of effect(s).

20 Further, the interpolation from Distilled and Distillation Residue Grades to Technical Grade proposed in the read-across/grouping justification document provided in IUCLID Section 13 contradicts your hypothesis of reading-across from Technical Grade to the Substance.

21 As explained in the section 1.2.2. below, there is no relevant supporting information which would allow to conclude on the proposed read-across approach for the algae toxicity while information on mammalian toxicity indicates that the Substance may cause greater toxicity than the analogue Technical Grade (see above). Furthermore this decision does not reject in general grouping of three substances into the category based on structural/compositional similarity of substances, however it rejects the read-across approach proposed where information from the analogue substance Technical grade is used to predict algae toxicity of the Substance for the reasons set in this decision.

22 Therefore you have not demonstrated and justified that the properties of the source substance and of the Substance are likely to be similar despite the observation of these differences.

1.2.2. Relevance of the supporting information

23 According to the Guidance on IRs and CSA, Section R.6.2.2.1.f., "it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals".

24 In order to support your claim that the Substance and source substance(s) have similar properties for the endpoints under consideration, you refer to the results of long-term sediment toxicity studies performed according to OECD TG 218, OECD TG 211 with Distilled Grade and Distillation Residue Grade, low bioaccumulation potential of non-polymeric constituents and to mammalian toxicity data indicating that "the data still follows a regular

pattern". You have not provided any evidence or justification as to how information on sediment, daphnids toxicity with Distilled Grade and Distillation Residue Grade as well as accumulation in fish and mammalian toxicity is relevant for the prediction of toxicity to aquatic plants from Technical Grade to Distilled Grade.

25 Accordingly, this information is not considered as relevant to support your hypothesis. As a consequence, you have not established a reliable basis for predicting the properties of the endpoints under consideration.

1.2.3. Adequacy and reliability of source studies

26 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 this case OECD TG 201 and the requirements of OECD GD 23 if the substance is difficult to test. Therefore, the following specifications must be met:

- 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.
- analytical monitoring is conducted. For UVCBs, it is to be demonstrated that concentrations were consistently maintained within 80-120% of the initial or mean measured values over the exposure duration (e.g. based on a comparison of the mass spectral full-scan GC or HPLC chromatogram peak area). Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided.

27 Your registration dossier provides an ISO 10253 study showing that no analytical monitoring of exposure was conducted and there is no justification why the analytical monitoring of exposure concentrations is not technically feasible provided.

28 In your comments to the draft decision you contest the conclusion that the current test is not valid and you clarify that it provides relevant data, as:

- the study was performed according to the principles of Good Laboratory Practice;
- the TOC analysis of the solutions was performed at 0 and 72 h, but the method was not sufficiently sensitive to discriminate between the exposure concentrations;
- due to "a clear concentration-response relationship for algal growth inhibition […] the test organisms were indeed exposed to the test substance at different WAF loading rates".
- the procedures of WAFs preparation were similar in OECD TG 211 study (with the Substance) and in the ISO 10253 (with Technical Grade), so "WAFs in the ISO 10253 study should have resulted in a concentration series of the soluble constituents of the test substance". However you note that "the duration of stirring the solutions differed depending on the nominal loading rate of the WAFs being prepared". E.g. 16 hours stirring was used for WAFs preparation with mid-depth siphoning in ISO 10253 study versus three days stirring with siphoning through the glass wool for the OECD TG 211 study.

29 As noted in your comments the reliable method for the preparation of test solutions and quantification of the test material (as was used in OECD TG 211) is available, however was not applied in the reported experimental study.

30 Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically it was not verified to what extent the test substance was present in the test solution during the test duration and whether or not the effect values

could be based on nominal concentrations. Even if the test organisms were allegedly exposed, these deficiencies result in difficulties with interpretation of the test results, including that they may result in an underestimation of the toxicity of the Substance.

31 Therefore, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameter(s) of the corresponding OECD TG.

1.2.4. Conclusion on the read-across approach

32 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

1.2.4.1. QSAR adaptation proposed in your comments to the draft decision

33 Furthermore in your comments to the draft decision you note that the available experimental study can provide supporting evidence and you indicate that you intend to adapt this information requirement according to Annex XI, section 1.3 (QSAR). You note that "OECD TG201 test procedure would only subsequently be conducted if the QSAR-based estimates for the growth inhibition in aquatic plants endpoint either:

- was not considered to be sufficiently reliable.
- indicated that algae were the most sensitive taxonomic group with regard to acute aquatic toxicity."

34 First, ECHA agrees that available study cannot be considered adequate to address standard information requirement alone.

35 Second, as your proposal to adapt this information requirement relies on QSAR data which is yet to be generated and documented, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

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

1.3. Study design and test specifications

37 The Substance is difficult to test due to the UVCB type, low water solubility (0.305 mg/L at 20 °C in OECD TG 105) and adsorptive properties (log Kow >6.2 in OECD TG 117). 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.

38 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).

39 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

2. Long-term toxicity testing on fish

40 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.

2.1. Information provided

41 You have provided the following information:

- an adaptation under Annex XI, Section 1.5. ('Grouping of substances and read-across'). In support of your adaptation, you provide the following information:
  (i) a study according to OECD TG 203 on the analogue substance Cashew (*Anacardium occidentale*) Nutshell Extract, Decarboxylated with EC List No. 941-216-3.

42 The information on long-term toxicity on fish for the Substance is described under section 3 of this Appendix below.

2.2. Assessment of the information provided

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

44 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).

45 In the provided OECD TG 105, the saturation concentration of the Substance in water was determined to be 0.305 mg/l at 20 °C.

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

47 The examination of the information provided on long-term toxicity on fish, comments to the draft decision as well as the selection of the requested test and the test design are addressed under section 3 of this Appendix below.

Reasons related to the information under Annex IX of REACH

3. Long-term toxicity testing on fish

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

3.1. Information provided

49 You have provided the following justification to omit the study: "There is no data on the long-term toxicity of Cashew Nutshell Extract, Decarboxylated, Distilled (Distilled Grade) to fish. Estimates of the relative short-term toxicity of cardanol (the major constituent of Distilled Grade) to different taxonomic groups have been obtained using the OECD QSAR Toolbox (Version 3.1). These in-domain supporting data, are considered to be reliable with restrictions (Klimisch Code 2). They indicate that invertebrates are more sensitive than algae (by a factor of 10.6 times), with fish being the least sensitive (by a factor of 19.3 times) taxonomic group. Data has been generated for the OECD TG211 Daphna magna Reproduction Test on Distilled Grade and shows that there were no effects on the reproduction (offspring number) and the development of juveniles (growth rate). This data was used to develop less precautionary Predicted No Effect Concentrations for fresh and marine waters and to conduct an updated Risk Characterisation Exercise described in the Chemical Safety Report. This risk assessment showed that for all the identified exposure scenarios all the Risk Characterisation Ratios (RCRs) for the aquatic compartment (fresh and marine waters) were all below 1 indicating the risks were controlled. On the basis of the absence of risks to the aquatic compartment from the identified uses of Distilled Grade it is not proposed that testing of the long-term toxicity to fish is conducted."

3.2. Assessment of the information provided

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

51 A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

52 Your justification to omit this information in your registration dossier does not refer to any legal ground for adaptation under Annex XI to REACH.

53 In your comments to the draft decision you note that you are aware that "the General Court will examine (inter alia) the correct interpretation of Column 2 of Annex IX, Section 9.1" and therefore you "requests that the Draft Decision is amended to remove this requirement subject to a definitive interpretation on the meaning of column 2 of section 9.1 of Annex IX from the General Court in due course".

54 The procedure before the General Court is not suspensive.Therefore, you have not demonstrated that this information can be omitted.

3.3. QSAR adaptation proposed in your comments to the draft decision

55 You indicate that you intend to adapt this information requirement according to Annex XI, section 1.3 (QSAR). You note that "OECD TG 210 test procedure would only subsequently be conducted if the QSAR-based estimates for the long-term toxicity to fish endpoint either:

- was not considered to be sufficiently reliable.

- indicated that fish were the most sensitive taxonomic group with regard long-term aquatic toxicity."

56 As your proposal to adapt this information requirement relies on QSAR data which is yet to be generated and documented, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

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

3.4. Study design and test specifications

58 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.).

59 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 1.3 of this Appendix above.

Reasons related to the information under Annex X of REACH

4. Pre-natal developmental toxicity study in a second species

60 Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is an information requirement under Annex X to REACH (Section 8.7.2.).

4.1. Information provided

61 You have adapted this information requirement by using Column 2 of Annex X, Section 8.7. Furthermore, you refer to REACH Annex XI and weight of evidence in your statement. To support the adaptation, you have provided following information:

i. Summary of justification: You consider that this waiver is justified taking into account the outcome of the first PNDT test and all other relevant available data of the test substance that shows no adversity on reproductive processes of mating and pregnancy or early development of the offspring. Furthermore, you postulate that the test substance probably does not cross the placental barrier. In addition the results of the Risk Characterisation Exercise covers all relevant exposures throughout the life cycle of the substance demonstrated an absence of significant risks in all scenarios of the manufacture and all identified uses to the general population including pregnant females (i.e. the Risk Characterisation Ratios were <1 in all instances). Therefore, your conclusion is that PNDT in a second species is not required given the weight of evidence of the currently available information for this endpoint.

ii. Oral gavage combined repeat dose study with reproduction/developmental toxicity screening in the rat with the Substance (OECD TG 422, 2005)

iii. Prenatal Developmental Toxicity Study of Cashew Nutshell Extract, Decarboxylated, Distilled by oral gavage in rats (OECD TG 414, 2019)

4.2. Assessment of the information provided

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

63 Under Section 8.7., column 2 of Annex X to REACH, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria:

- that there is no evidence of toxicity seen in any of the tests available;
- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and
- that there is no or no significant human exposure.

64 Firstly, the source of information (iii.) shows that all dams were terminated due to severe toxicity of the test substance at the highest dose of 1000 mg/kg bw/day.

65 Secondly, there is no toxicokinetic data available that systemic absorption would not occur.

66 Thirdly, the IUCLID dossier contais numerous professional and consumer uses of the substance, which you have not addressed. Also, the large variety of exposure scenarios potentially leads to significant human exposure.

67 The source of information (iii.) shows evidence of toxicity. Furthermore, the criteria refers to evidence of toxicity, not specifically to adverse effects on fertility and developmental toxicity.

68 You have not provided toxicokinetic data to show that there is no systemic absorption and the experimental in vivo data demonstrates the opposite. Furthermore, the uses of the Substance does not exclude significant potential human exposure.

69 Therefore, your adaptation is rejected.

70 ECHA further examined below your weight of evidence adaptation. Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

71 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.

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

73 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.

74 Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

75 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

76 None of the sources of information provide relevant information on a second species.

77 Your weight of evidence adaptation does not include any relevant sources of information to conclude on the property of prenatal developmental toxicity on a second species.

78 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 an OECD TG 414 study on a second species.

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

4.3. Assessment of comments to the draft decision

80 In your comments to the draft decision you agree to perform the requested study as the test is an information requirement at Annex X.

4.4. Specification of the study design

81 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species. The study in the first species was carried out by using a rodent species (rat).

82 Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

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

84 Based on the above, the study must be conducted in rabbits with oral exposure of the Substance.

5. Extended one-generation reproductive toxicity study

85 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X to REACH (Section 8.7.3.).

5.1. Information provided

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

i. Oral gavage combined repeat dose toxicity study with reproduction/developmental toxicity screening in the rat (2005) with the Substance..

ii. A 90-Day Study of Cashew Nutshell Extract, Decarboxylated, Distilled (Distilled Grade) by Oral Gavage in Wistar Han Rats (2019) with the Substance.

iii. Prenatal Developmental Toxicity Study of Cashew Nutshell Extract, Decarboxylated, Distilled (Distilled Grade) by Oral Gavage in Rats (2019) with the Substance.

iv. Prenatal Developmental Toxicity Study of Cashew Nutshell Extract, Decarboxylated, Distillation Residue (Distillation Residue Grade) by Oral Gavage in Rats (2019) with Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distillation Residue Grade, EC No. 941-212-1.

v. A 90-Day Study of Cashew Nutshell Extract, Decarboxylated, Distillation Residue (Distillation Residue Grade) by Oral Gavage in Wistar Han Rats (2019) with Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distillation Residue Grade, EC No. 941-212-1.

vi. Milk yield and/or milk quality improving agent, perinatal disease preventive or therapeutic agent, and reproductivity improving agent for ruminant (2016) with CNSL Technical Grade.

87 Furthermore, you provide "endpoint level" justification in the IUCLID registration dossier for adoption of a category approach for the three grades of processed Cashew Nutshell Extract, in Section 7.8.1.: "It is considered appropriate to read-across from the data for Distillation Residue Grade to Distilled Grade as part of a weight of evidence approach for the EOGRTS information requirement.". You have provided a justification document in IUCLID Section 13.

88 Based on the presented sources of information, you argue that the available data gives sufficient information to conlude on the reproductive toxicity because: "Although the conduct of the EOGRTS test could potentially provide additional data on reproductive and developmental toxicity endpoints it would not improve the overall conclusions on the perceived risks posed to human health by exposure to the test substance via the identified exposure scenarios in the Chemical Safety Report. In addition, studies show that general systemic toxic effects only occur in the presence of local effects due to the known irritancy of the test substance. Therefore, sustained dermal exposure which could potentially lead to systemic effects in workers and consumers is not to be expected without significant local effects. This would limit the total dose to which individuals would be exposed.".

89 Furthermore, you support your WoE argumentation by stating: "[…]There are no Specific Rules for Adaptation from Column 1 in Annex X Section 8.7 of the REACH Regulation, but these are in place for the test at Annex IX. However, adaptions pursuant to Annex XI (General Rules for Adaptation of the Standard Testing Regime set out in Annexes VII to X) and a recent Judgement of the General Court in Case T-755/17 (September 2019) in relation to the Principle of Proportionality are considered relevant to the potential for adaption of this test requirement in appropriate instances.

90 Paragraph 287 of the Judgement states that: "The relevant criterion relating to the principle of proportionality is the result of balancing the different objectives pursued by Regulation No 1907/2006 and the application of the precautionary principle. In accordance with that criterion, in order to justify a request to conduct testing, the ECHA must not only demonstrate the existence of a potential risk for human health and the environment, and the necessity to clarify that risk, but also establish that there is a realistic likelihood that the information requested would allow improved risk management measures to be taken"."

91 You further claim that ECHA must follow similar conditions in this case, referring to the Board of Appeal's decision in case A-008-2017.

5.2. Assessment of the information provided

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

93 Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

94 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.

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

96 You refer to the proportionality principle, to the Judgement of the General Court in Case T-755/17 and to the Board of Appeal's decision in case A-008-2017. However, these last two cases are irrelevant because they concern the Substance Evaluation process, not Dossier Evaluation, as in this case. The rules and the aim of these two processes are different. Dossier Evaluation, under which this decision is, aims to identify intrinsic properties of a substance and further, assess the hazardous properties of a substance. Under Dossier Evaluation, the proportionality principle is embedded in the information requirements and

the adaptations provided under Annexes VI to XI. Therefore, ECHA has the duty to implement REACH and request testing for standard information requirements in case of non-compliant information.

97 You have not included a justification for your weight of evidence adaptation, 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.

98 Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

99 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex X includes similar information that is produced by the OECD TG 443 design as specified in this decisions. At general level, it includes information on 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity, - and 4) if column 2 triggers are met, also information on sexual function and fertility of the offspring, toxicity to F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

100 This is based on hazards and therefore any comment on exposure or risk is not relevant.

5.2.1. Sexual function and fertility

101 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, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

102 Sources (i., ii., v.) provide relevant information on organ weights and histopathology of reproductive organs in both sexes. Sources (i., iii., iv.) provide relevant information on maintenance of pregnancy. Source (vi.) does not provide relevant information.

103 Therefore, the only relevant information is on limited aspects of sexual function and fertility: organ weights and histopathology of reproductive organs and maintenance of pregnancy.

104 Furthermore, the sources of information have deficiencies that reduce the reliability.

105 First, information from source substance(s) can be used as part of weight of evidence adaptation if the read-across is accepted.

106 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

107 Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents.

108 You have provided a read-across justification document in IUCLID Section 13.

109 You predict the properties of the Substance from the structurally similar substance: Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, Distillation Residue Grade, EC No. 941-212-1 and Technical Grade Cashew (Anacardium occidentale) Nutshell Extract, Decarboxylated, EC List No. 941-216-3. i.e. the source substances.

110 The source study (iii.) that you have used in your read-across approach, Prenatal Developmental Toxicity Study of Cashew Nutshell Extract, Decarboxylated, Distillation Residue (Distillation Residue Grade) (2019), corresponds to a guideline title performed similar/according to the OECD TG 414.

111 The source study (iv.) that you have used in your read-across approach, A 90-Day Study of Cashew Nutshell Extract, Decarboxylated, Distillation Residue (Distillation Residue Grade) (2019), corresponds to a guideline title performed similar/according to the OECD TG 408 and has a duration of 90 days.

112 The source study (v.) that you have used in your read-across approach, Milk yield and/or milk quality improving agent, perinatal disease preventive or therapeutic agent, and reproductivity improving agent for ruminant (2016) with CNSL Technical Grade, provides information on milk quality and has a duration 5 days from the date of calving.

113 You have provided the following reasoning for the prediction of toxicological properties: "The three grades of processed Cashew Nutshell Extract is the commonality of the constituents and functional groups in the three grades and the common modes of action for specific localised endpoints that are manifest in physico-chemical, environmental fate and toxicological properties that are similar or follow a regular pattern as a result of structural similarity."

114 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 substance.

115 For the same reasons explained under Sections 1.2.1. and 1.2.2., the information on the analogue substances do not provide reliable information for weight of evidence. Therefore, the information from the analogue substance(s) submitted under your weight of evidence adaptation is not considered reliable and do not contribute to the weight of evidence adaptation.

116 Second, OECD TG 443 includes the following specifications:

- at least 20 pregnant females per dose group in parental P0 generation;
- examination of relevant life stages.

117 The source of information (i.) include only 10 pregnant females in each dose and control group.

118 In sources (iii., iv.) the animals were exposed from GD6 onwards, in sources (ii., v.) animals were not mated at all and in source (i.) the animals were exposed two weeks before mating and until post-natal day 4. None of the sources cover full spermatogenesis/folliculogenesis.

5.2.2. Toxicity to the offspring

119 Toxicity to offspring must cover information on deaths before, during or after birth, growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, organ weights and histopathology of reproductive organs and tissues in adulthood and other potential aspects of toxicity to offspring.

120 Only sources (i., iii., iv. and vi.) provides partially relevant information on toxicity to the offspring until post-natal day 4 (i.), before birth (iii., iv.) or during lactation (vi.).

121 Sources (ii. and v.) do not provide any information on toxicity to offspring, as they are repeated toxicity studies with no investigations on matings and offspring.

122 Therefore, the only relevant sources of information (i., iii., iv., vi.) contain information on a limited aspect of toxicity to offspring: toxicity before birth (deaths and growth before

birth, and malformations) or until postnatal day 4, but not on toxicity after birth up to adulthood as foreseen to be investigated in an OECD TG 443 (deaths, growth, clinical signs, sexual maturity, oestrous cyclicity, organ weights and hispathology of reproductive organs in adulthood).

123 Furthermore, the sources of information have deficiencies that reduces the reliability.

124 Exposure must cover all the life stages foreseen to be exposed in the information requirement as specified under OECD TG 443.

125 None of these relevant studies covered period of full exposure of the F1 generation up to adulthood as in sources (iii.-iv.) there was no exposure postnatally and sources of information (i., iv.) do not follow the F1 generation up to adulthood. The source (vi.) covers only 5 days lactational exposure period.

5.2.3. Systemic toxicity

126 Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and histopathology of non-reproductive organs and tissues (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

127 Only the sources of information (i.-v.) provide relevant information on clinical signs, survival and body weights in parental P generation.

128 There is no information at all on systemic toxicity of the F1 generation up to adulthood.

129 Therefore, the only relevant information for systemic toxicity (for P generation) are the sources of information (i.-v.). However, as indicated above there is no information at all on systemic toxicity of the F1 generation up to adulthood.

130 Further, the reliability of sources of information (i.-v.) are affected by the issues mentioned above.

131 Because of that it is not possible to conclude if the Substance has or has not an effect on the systemic toxicity (during pregnancy).

5.2.4. Information on triggered investigations

132 If column 2 triggers are met, information on sexual function and fertility of the offspring, developmental toxicity in F2 generation is relevant. Sexual function and fertility of the offspring includes the same key investigations than in P0 animals (above section "sexual function and fertility") and developmental toxicity in F2 generation includes investigations up to weaning similar to F1 generation.

133 There is no source of information which investigates sexual function and fertility in the F1 generation (producing the F2 generation). However, the criteria at Annex X section 8.7.3 column 2 are met (see below) and therefore this relevant information is missing.

5.2.5. Conclusion

134 Taken together, the relevant sources of information as indicated above, provide only limited information on

- Sexual function and fertility on parental P0 generation but its reliability is significantly affected by no sufficient exposure duration and statistical power.
- Toxicity to offspring, but not covering relevant information on life stages of the F1 generation (postnatal period up to adulthood) and its reliability is significantly affected.

- Systemic toxicity, not covering relevant information on life stages of the F1 generation (postnatal up to adulthood), and its reliability is significantly affected.

135 There is no information on sexual function and fertility of the offspring, developmental toxicity in F2 generation.

136 Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on sexual function and fertility, toxicity to offspring, systemic toxicity and developmental toxicity in F2 generation in order to conclude on these aspects.

137 Finally, 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 an OECD TG 443 study as specified in this decision.

138 Therefore, your adaptation is rejected.

5.3. Assessment of comments to the draft decision

139 In your comments to the draft decision, the Consortium recognises the missing key investigations in the provided data and you agree to conduct the requested study. The proposed extension of the deadline is addressed in Appendix 2.

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

5.4. Specification of the study design

5.4.1. Species and route selection

141 A study according to the test method OECD TG 443 must be performed in rats with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

5.4.2. Pre-mating exposure duration

142 The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

143 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

144 In this specific case, ten weeks exposure duration is supported by the lipophilicity of the Substance (Log K_{ow} = 6.2) to ensure that the steady state in parental animals has been reached before mating.

145 Therefore, the requested pre-mating exposure duration for the P0 animals is ten weeks.

5.4.3. Dose-level setting

146 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

147 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

148 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

149 In summary: Unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) (2 in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(4) the highest dose level in P0 animals must follow the limit dose concept.

150 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

151 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

5.4.4. Cohorts 1A and 1B

152 Cohorts 1A and 1B belong to the basic study design and must be included.

153 Splenic lymphocyte subpopulation analysis

154 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, para. 66; OECD GD 151, Annex Table 1.3).

155 Investigations of sexual maturation

156 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, para. 12 in conjunction with OECD TG 443, para. 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

5.4.5. Extension of Cohort 1B

157 If the Column 2 conditions of 8.7.3. are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

158 The extension is required, among others, if the use of the Substance is leading to significant exposure of consumers and professionals (column 2, first para., point (a) of Section 8.7.3.) and if there are indications that the internal dose for the Substance will reach a steady state

in the test animals only after an extended exposure (column 2, first para., point (b), second indent of Section 8.7.3.

159 The use of the Substance reported in the joint submission is leading to significant exposure of consumers and professionals because the Substance is used by professionals as mixing or blending in batch processes, transfer of substance or mixture (charging and discharging) at non-dedicated facilities, transfer of substance or mixture (charging and discharging) at dedicated facilities, roller application or brushing, non industrial spraying, treatment of articles by dipping and pouring, hand-mixing with intimate contact and only PPE available (PROCs 5, 8a, 8b, 10, 11, 13, 19) and consumers as coatings and paints, thinners and paint removes.

160 Furthermore, there are indications that the internal dose for the Substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure. Specifically, the logKow for the substance is above 4.5 indicating potential accumulation.

161 For the reasons stated above, Cohort 1B must be extended.

162 Organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, para. 67 and 72) because there is a concern for reproductive toxicity/endocrine activity indicated by the toxicity-triggers to extend the Cohort 1B.

163 The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151.

5.4.6. Cohorts 2A and 2B

164 The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.

165 Existing information on the Substance itself derived from available *in vivo* study (OECD TG 408 (2019)) shows evidence of thyroid toxicity. In particular, for males, the study shows a consistent picture of statistically significantly increased TSH and decreased T4 levels, accompanied by dose-dependent increase in the incidence of follicular cell hypertrophy. For females, there are also signs of perturbation of thyroid hormones (including increased TSH).

166 According to Guidance on IRs & CSA, Appendix R.7.6-2, relevant changes in thyroid hormone levels or signs of thyroid toxicity indicating such changes are a particular concern justifying inclusion of the developmental neurotoxicity cohorts. It is further explained inAppendix A of the ECHA/EFSA ED Guidance[2] that "1. Substances inducing histopathological changes (i.e. follicular cell hypertrophy and/or hyperplasia and/or neoplasia) in the thyroid, with or without changes in the circulating levels of THs, would pose a hazard for human thyroid hormone insufficiency in adults as well as pre- and post-natal neurological development of offspring." and "2. Substances that alter the circulating levels of T3 and/or T4 without histopathological findings would still present a potential concern for neurodevelopment.". Therefore, the effects observed in the OECD TG 408 study in males and females are biologically meaningful. In line with the Guidance on IRs & CSA, Appendix R.7.6-2, they show a particular concern justifying inclusion of the developmental neurotoxicity cohorts.

[2] EFSA/ECHA (2018) Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 16(6):e05311

167 For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

5.4.7. Cognitive functions: learning and memory

168 Paragraph 51 of OECD 443 provides that, "If existing information indicates the need for other functional testing (e.g. sensory, social, cognitive), these should be integrated without compromising the integrity of the other evaluations conducted in the study."

169 The Substance caused changes in thyroid histopathology as well as thyroid hormone level in the OECD TG 408 study, and so perturbs thyroid hormone signalling. It is known that perturbation of thyroid hormone signalling in offspring affects spatial cognitive abilities (learning and memory) [1-3].

170 Therefore, it is necessary to conduct spatial learning and memory tests for F1 animals. The spatial learning and memory tests must be performed in accordance with OECD 426 paragraph 37, i.e. at adolescence (e.g. PND 25±2 days) and young adulthood (PND 60 and older).

[1] Axelstad *et al*. (2008) Developmental neurotoxicity of Propylthiouracil (PTU) in rats: Relationship between transient hypothyroxinemia during development and long-lasting behavioural and functional changes. *Toxicol. Appl. Pharmacol.* 232, 1-13.

[2] van Wijk *et al*. (2008) Perinatal and chronic hypothyroidism impair behavioural development in male and female rats. *Exp. Physiol.* 93, 1199-1209.

[3] Amano *et al.* (2018) Effects of Mild Perinatal Hypothyroidism on Cognitive Function of Adult Male Offspring. *Endocrinol.* 159(4), 1910-1921.

5.4.7.1. *Observations for the spatial learning and memory testing*

171 OECD TG 426, paragraph 37 presents examples of test methods for different types of associative learning and memory. Among the tests given in OECD TG 426, paragraph 37, you should conduct the Morris water maze test or Radial arm maze test at one time point, and the Cincinnati water maze test at the other time point to investigate spatial learning and memory, as these appear to be the most sensitive tests [4-7].

172 Investigations of spatial learning and memory should not compromise the integrity of the study. In OECD TG 443 adverse effects on sexual function and fertility may limit the number of offspring available for developmental investigations. Dosing must be based on the considerations provided above ('Dose-level setting'), and dosing must not be lowered in order to get a sufficient number of offspring. The priority of the OECD TG 443 test is to identify potential effects on sexual function and fertility.

173 Taking into account the practical aspects of conducting the OECD TG 443 study, as an alternative to Cohort 2A, the investigations on spatial learning and memory may also be conducted in Cohort 1A animals which can be allocated to two sets of animals, 10 males and 10 females in both; the first set of animals to be tested at adolescence and the other set of animals at young adulthood.

[4] Levin E. (2015) Learning about cognition risk with the radial-arm maze in the developmental neurotoxicology battery. *Neurotoxicol Teratol.* 52, 88-92.

[5] Vorhees and Williams (2015) Reprint of "Value of water mazes for assessing spatial and egocentric learning and memory in rodent basic research and regulatory studies". *Neurotoxicol Teratol.* 52, 93-108.

[6] Vorhees and Makris (2015) Assessment of learning, memory, and attention in developmental neurotoxicity regulatory studies: synthesis, commentary, and recommendations.

Neurotoxicol Teratol. 52, 109-115.

[7] Vorhees and Williams (2016) Cincinnati water maze: A review of the development, methods, and evidence as a test of egocentric learning and memory. *Neurotoxicol Teratol*. 57, 1-19.

5.5. Further expansion of the study design

174 No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3 if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

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 28 August 2021.

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

In your comments to the draft decision, you raised several procedural observations. These have been acknowledged and replied to you in a separate REACH-IT message.

In your comments on the draft decision, you requested an extension of the deadline to provide information.

You have contacted two laboratories that can successfully deliver an EOGRTS test and the shortest deadline to deliver the data is estimated to be early to mid 2025. Considering the foreseen timeline to publish the final decision and current issue with laboratory capacity, your request is justified.

On this basis, ECHA has extended the deadline to 36 months.

ECHA took into account your comments and did not amend the request(s) but amended the deadline.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

In your comments you agreed to the proposed amendment(s). Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee unanimously agreed on the draft decision in its MSC-78 written procedure. ECHA adopted the decision under Article 51(6) 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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[3].

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

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

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