~~Confidential~~

Helsinki, 19 November 2021

Addressees
Registrant(s) of alcohol C16 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
17/09/2018

Registered substance subject to this decision ("the Substance")
Substance name: Hexadecan-1-ol
EC number: 253-149-0
CAS number: 36653-82-4

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 ***24 February 2026***.

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

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

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

2. 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;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

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

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes X of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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 Christel Schilliger-Musset, 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.

Appendix on Reasons common to several requests

(i) Assessment of your weight of evidence adaptation under Annex XI, Section 1.2

You seek to adapt the following standard information requirements by applying (a) weight of evidence approaches in accordance with Annex XI, Section 1.2:

- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

ECHA has considered the scientific and regulatory validity of your weight of evidence approach in general before assessing the specific standard information requirements in the following appendices.

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.

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.

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

You have provided summaries in separate endpoint study records for reproductive and developmental toxicity. In those summaries you briefly present each of the sources of information, describe the results and conclude that this information can be used for weight of evidence to predict the toxicological properties of the Substance for reproductive toxicity: "*The conclusion that the members of the aliphatic alcohol category (C6 to C24) are not expected to impair fertility is based on a weight of evidence approach using data from reproductive screening studies [C12 (dodecan-1-ol), C18 (octadecan-1-ol)], a fertility study [C22 (docosan-1-ol)], together with a lack of effect on the reproductive organs in repeat dose studies over the range of linear and essentially linear alcohols*." …"*Based on this it is concluded that hexadecan-1-ol is not expected to impair fertility*." and for developmental toxicity: "*Therefore, based on the weight of evidence from other alcohols across the category, it is concluded that hexadecan-1-ol is unlikely to cause developmental effects*".

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.

Your adaptation is rejected because lack of adequate and reliable (concise) documentation for justification and the information requirement is not fulfilled.

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.

Your weight of evidence adaptation 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 Appendices below.

Reliability of the provided information with analogue substances

ECHA understands that you intend to predict the (eco)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.

Grouping of substances and read-across approach

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 (addressed under 'Scope of the grouping'). Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

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

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group (category) of 'C6-24 Alcohols. Long Chain Aliphatic Alcohols (C6-24 primary aliphatic alcohols; linear and essentially linear) (LCAAs)'. You have provided a read-across justification document in IUCLID Section 13.

You provide the following reasoning for the grouping the substances: "*The hypothesis is that the long chain linear aliphatic alcohol Category has, at its centre, an homologous series of increasing carbon chain length alcohols […] The structure of the Category is associated with a consistency and predictability in the physicochemical, environmental, and toxicological property data across its members. In addition, certain branched and unsaturated structures are considered to have such similar properties that their inclusion in the category is well justified.".*

You define the applicability domain of the category as follows: "*This category applies to linear and essentially-linear primary aliphatic alcohols within a carbon chain length range of C6-C24"*.

In your comments to the initial draft decision you propose to include the analogue substance (Z)-octadec-9-enol (EC no. 205-597-3) into the category. You also provide a proposal for category members to be further tested to obtain a satisfactory data density within the category for the relevant endpoints of this decision, and to justify the inclusion of the additional category member.

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

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

B. Predictions for properties

You have provided the following reasoning for the prediction of toxicological properties: " *The family consists of alcohols with various compositions and structures […]. The structure of the Category is associated with a consistency and predictability in the physicochemical, environmental, and toxicological property data across its members. In addition, certain branched and unsaturated structures are considered to have such similar properties that their inclusion in the category is well justified".*

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.

You intend to predict the properties for the category members from information obtained from the following source substances:

Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

- Docosan-1-ol, EC#211-546-6;
- 3-methylbutan-1-ol, EC#204-633-5;
- C24-34 even chain alcohols;
- Substance candidates for developmental toxicity testing in a second species (OECD Test Guideline 414): C6 and C14.

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

- Octadecan-1-ol, EC 204-017-6, similar to OECD 422;
- Dodecan-1-ol, EC 203-982-0, similar to OECD 422;
- Docosan-1-ol, EC 211-546-6, similar to OECD 415;
- Hexadecan-1-ol, EC 253-149-0, non-TG/GLP;
- Hexan-1-ol, EC 203-852-3, non-TG/GLP;
- Alcohols, C14-15, EC 616-261-4, non-TG/GLP
- Alcohols, C10-16, EC 267-019-6, similar to OECD 408
- Docosan-1-ol, EC 211-546-6, non-TG/GLP;
- Substance candidates for extended one-generation reproductive toxicity testing (OECD Test Guideline 443): *"C6, C14 are possible good candidates but the final selection will be confirmed with results from screening tests".*

ECHA notes the following shortcoming(s) with regards to prediction(s) of toxicological properties.

1. Data density

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.*

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[4] To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.1.5.

Furthermore in larger categories there may be breaks in trends which could affect the reliability of interpolation.[5] To confirm that there are no such breakpoints, adequate and reliable information needs to cover also substances within a range of homologous series.

In your dossier you have provided PNDT studies in a second species for one category member, and two source substances outside the category boundaries (3-methylbutan-1-ol, EC#204-633-5; C24-34 even chain alcohols) which are on or outside the upper and lower borders of the category, respectively. Based on these studies you claim that there is consistent absence of pre-natal toxicity in a second species across the category (see request A.1).

In your comments to the initial draft decision you state that you intend to perform PNDT studies with substance candidates for C6 and C14 in a second species to have results with category members with low, middle and high-chain length. ECHA agrees that such testing will improve the data density but the information in your comments is not sufficient for ECHA to make an assessment under Section 1.5 of Annex XI of REACH, because the studies are not yet available. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

You have not provided any extended one-generation reproductive toxicity study (OECD TG 443), or two-generation reproductive toxicity study (OECD TG 416) conducted before 13.03.2015.

In your comments to the initial draft decision you state that you intend to perform EOGRT studies with substance candidates for C6 and C14. ECHA notes that using those category members for testing will bring results with low and middle chain length but no EOGRT study on a category member with high-chain length. Furthermore, for C8-C11 there will be no information from an EORGT study or a screening for reproductive/developmental toxicity study (similar to OECD TG 421 or 422).

In your comments you also state your intention to include the analogue substance (Z)-octadec-9-enol (EC no. 205-597-3) into the category. You acknowledges the need for strengthening the read-across justification and implementing bridging strategy in order to confirm the inclusion of (Z)-octadec-9-enol to the Category of C6-24 linear and essentially-linear aliphatic alcohols. Therefore, you intend to conduct a combined repeated dose toxicity studywith the reproduction/developmental toxicity screening test (OECD Test Guideline 422) with (Z)-octadec-9-enol in order to confirm the inclusion of the substance to the Category. You note that in case different effects were observed in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD Test Guideline 422) with (Z)-octadec-9-enol, this would indicate that further higher tier testing is necessary as read-across based on a category for those properties may not be sufficient.

ECHA agrees that this approach may improve the category . However, as indicated above, the information in your comments is not sufficient for ECHA to make an assessment under Section 1.5 of Annex XI of REACH, because the studies are not yet available. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

ECHA concludes that you have not yet demonstrated that the information for the members is sufficient to address the uncertainties and to establish a trend across the category consisting

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.2.

of eight substances. Furthermore, in the absence of information on substances between the upper and lower borders of the category, it cannot be confirmed that there is no change in toxicity within the given range of chain length or as a result of unsaturation. Therefore, the information provided is not sufficient to conclude that toxicological/ecotoxicological properties are likely to follow a regular pattern.

Conclusions on the grouping of substances and read-across approach

As explained above, you have not established, neither in your registration dossier nor in your comments, that relevant properties of the Substance can be predicted from data on the analogue substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Endpoint-specific shortcomings affecting the reliability

Further endpoint-specific shortcomings affecting the reliability of the weight of evidence approach are detailed in the reasoning in Appendix A.

Appendix A: Reasons to request information required under Annex X of REACH

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

Pre-natal developmental toxicity study in a second species is a standard information requirement in Annex X to REACH.

ECHA understands that you submitted a weight-of-evidence adaptation under Annex XI, Section 1.2 of REACH by stating: *"In accordance with Section 1 of Annex IX, a developmental toxicity study in rabbits (as required in Section 8.7.2) is scientifically unjustified.."*

You have provided the following sources of information in rabbit:

i. 2002 Prenatal Developmental Toxicity Study in rabbits (Similar to OECD TG 414) on source substance *Docosan-1-ol*, EC 211-546-6.
ii. 1995 Prenatal Developmental Toxicity Study in rabbits (OECD TG 414) on source substance *3-methylbutan-1-ol*, EC 204-633-5.
iii. 1998 Developmental Toxicity study in rabbits (Non-TG) on source substance *C24-34 even chain alcohols*.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In order to allow concluding on no prenatal developmental toxicity in two species for the Substance in a weight of evidence adaptation, the justification must cover the key elements foreseen to be investigated in an OECD TG 414 study in two species. The following aspects of this guideline include: 1) prenatal developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

ECHA has assessed to what extent the information submitted enables a conclusion of hazardous properties for prenatal developmental toxicity in a second species and identified the following deficiencies:

While the sources of information (i.-iii.) provide relevant information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy, these sources of information have the following deficiencies affecting their reliability.

First, the conditions of OECD TG 414 include having 20 female animals with implantation sites for each test and control group and exposure duration from implantation to the day prior to scheduled caesarean section.

Study (i.) had duration of treatment during days 6-19 of gestation as the termination was on day 29 of gestation. Study (ii.) had duration of treatment during gestation days 7 to 19 and only 15 pregnant femals per dose level. Study (iii.) had duration of treatment during days 6-18 of gestation and only 16 pregnant animals in low dose group and 17 in mid dose group. Therefore, these studies do not fulfil the conditions as foreseen in OECD TG 414.

Second, as explained in the Appendix on reasons common to several requests, the reported read-across approach does not fulfil the criteria in Annex XI, Section 1.5. Therefore, studies (i. – iii.) cannot be used as part of weight-of-evidence adaptations according to Annex XI, Section 1.2. In your comments to the initial draft decision you acknowledge the need for strengthening the evidence for this endpoint but would propose to support the toxicity

information requirements of the C6-C24 within the category context using a targeted testing approach.

Therefore, sources of information (i) to (iii) provide information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy in a second species, but that information is not reliable.

The targeted testing approach proposed in your comments to the initial draft decision is addressed in the *Appendix on reasons common to several requests*.

In conclusion, none of the provided sources of information alone or together allows to conclude whether the Substance has or has not hazardous properties related to prenatal developmental toxicity in a second species. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Information on study design

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

The study shall be performed with oral[6] administration of the Substance.

2. Extended one-generation reproductive toxicity study

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information:

i. 1992 Combined repeated dose with screening for reproductive/developmental toxicity study in rats (similar to OECD TG 422) with source substance *Octadecan-1-ol,* EC 204-017-6.
ii. 1992 Combined repeated dose with screening for reproductive/developmental toxicity study in rats (similar to OECD TG 422) with source substance *Dodecan-1-ol,* EC 203-982-0.
iii. 2002 One-generation reproductive toxicity study in rats (similar to OECD TG 415) with source substance *Docosan-1-ol,* EC 211-546-6.
iv. 1966 13-week study in rats (non-TG/GLP) with source substance *Hexadecan-1-ol,* EC 253-149-0.
v. 1966 13-week study in rats (non-TG/GLP) with source substance *Hexan-1-ol*, EC 203-852-3.
vi. 2002 26-week study in rats (non-TG/GLP) with source substance *Docosan-1-ol,* EC 211-546-6.
vii. 1978 Sub-chronic toxicity study in rats (similar to OECD TG 408, non GLP) with source substance *Alcohols, C14-15,* EC 616-261-4.
viii. 1983 Sub-acute toxicity study in rats (similar to OECD TG 407, GLP not specified) with source substance *Hexadecan-1-ol,* EC 253-149-0.

[6] ECHA Guidance R.7a, Section R.7.6.2.3.2.

ix. 1984 14-day study in male rats (non-TG/GLP specified) with source substance *Alcohols, C10-16,* EC 267-019-6.
x. 1996 13-week study in dogs (non-TG/GLP specified) with source substance *Hexadecan-1-ol,* EC 253-149-0.

In your comments to the initial draft decision you acknowledge that the available reproductive data currently do not fulfil Annex X data requirements, and therefore extended one-generation reproductive testing is required. You propose to support the toxicity information requirements of the C6-C24 within the category context using a targeted testing approach.

In your comments to the initial draft decision, you indicate that ECHA may not have evaluated your updated waiver for EOGRTS, where you conclude that "*There has been no indication of treatment-related effects on reproductive organs or tissues in any of the repeat dose toxicity studies, reproductive toxicity screening studies and prenatal developmental toxicity studies available for this or structurally analogous alcohols within the chemical category*". ECHA has assessed the information available in the registration dossier before the notification of the draft decision. Although the waiver is not summarised in this request, the Weight of Evidence evaluation below assesses all relevant information in the studies submitted for this endpoint, which together constitute the basis for the arguments in the waiver which was presented as a weight of evidence adaptation. This evaluation covered the additional details provided in the updated waiver, which described in more details the findings in the existing studies, although without these details changing ECHA's evaluation, including the rejection of the read-across and the weight of evidence for the reasons described below.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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 decision. At general level, it included 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.

Sexual function and fertility

Description of information required in more detail (relevance and coverage)

Sexual function and fertility on both sexes must cover 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.

The sources of information (i. - iii.) provide relevant information on sexual function and fertility, in particular, regarding functional fertility on males and females and investigations of reproductive organs. Repeated dose toxicity studies (iv. - viii., x.) provide relevant information on integrity of reproductive organs on both sexes, study (ix.) only in males.

However, the following deficiencies affect their reliability.

a) Functional fertility and histopathology of reproductive organs and tissues must be investigated in parental P0 animals as indicated in OECD TG 443 after at least ten weeks premating exposure duration if extension of Cohort 1B is not included to ensure the exposure of full spermatogenesis and folliculogenesis before mating.

In the case of your Substance, the conditions to include the extension of Cohort 1B are currently not met. The source of information (i. and ii.) investigates sexual function and fertility with the premating exposure duration of two weeks for the parental P0 animals, the source of information (iii.) has premating exposure duration of 15 days for female P0 animals, 71 days for male P0 animals. The other sources (iv.- x.) inform only about reproductive organs without mating of animals.

Therefore, the condition above is not met.

b) With regard to the information from analogue substances, used as part of WoE, read-across adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.5. are fulfilled. However, as explained in the Appendix on reasons common to several requests, the reported read-across approach does not fulfil the criteria in Annex XI, Section 1.5. In your comments to the initial draft decision you acknowledge that the available reproductive data currently do not fulfil Annex X data requirements, and therefore extended one-generation reproductive testing is required. You propose to support the toxicity information requirements of the C6-C24 within the category context using a targeted testing approach.

Therefore, studies (i.-iv., vi.-x.) cannot be used as part of weight of evidence adaptation according to Annex XI, Section 1.2.

In the absence of reliable information on sexual function and fertility with sufficient premating exposure duration for both parental P0 animals, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

Therefore, the condition above is not met.

Toxicity to offspring

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

The sources of information (i. - iii.) provide relevant information on to the offspring up to postnatal day 5 (i., ii.) and up to gestation day 20 (iii.), but have the following deficiencies affecting their reliability.

a) Under OECD TG 443, a study is to inform on toxicity to the offspring up to the adulthood, such as sexual maturity, oestrous cyclicity and histopathology of reproductive organs in adulthood.

None of the sources of information (i.- iii.) inform on toxicity to the offspring up to the adulthood. The sources of information (iv. – x.) investigate only adult animals without producing offspring and therefore are lacking information on offspring.

Therefore, information provided on toxicity to offspring do not cover sufficient duration of the study period.

Therefore, the condition above is not met.

b) The studies on analogue substances cannot be used as part of the weight of evidence adaptations for the reasons discussed above.

Therefore, the condition above is not met.

Systemic toxicity and information on F2 and DNT/DIT cohorts

ECHA considers that information on general organ toxicity, haematology and clinical chemistry is sufficiently available from provided studies (i.-x.) and column 2 triggers for F2 or additional cohorts are currently not met. Therefore the latter are not covered under the current evaluation.

The studies on analogue substances cannot, however, be used as part of a weight of evidence adaptations for the reasons discussed above.

In the absence of reliable information on toxicity to offspring up to the adulthood, no conclusion can be drawn on toxicity to offspring as required by the information requirement.

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

- Sexual function and fertility on parental P0 generation but their reliability is significantly affected for the reasons provided above.
- Toxicity to offspring, but their reliability is significantly affected for the reasons provided above.
- Systemic toxicity, but their reliability is significantly affected for the reasons provided above.

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

The targeted testing approach proposed in your comments to the initial draft decision is addressed in the *Appendix on reasons common to several requests*.

Conclusion on the WoE adaptation

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 with a design described in this decision.

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

<u>The specifications for the study design</u>

Premating exposure duration and dose-level setting

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

Ten weeks premating 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. [7]

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

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

Cohorts 1A and 1B

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

The study must be performed in rats with oral[8] administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the 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 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 ECHA Guidance[9].

[7] ECHA Guidance R.7a, Section R.7.6.
[8] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[9] ECHA Guidance R.7a, Section R.7.6.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[10].

B. Test material

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

1. Selection of the Test material(s)

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[11].

[10] https://echa.europa.eu/practical-guides
[11] https://echa.europa.eu/manuals

Appendix C: 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 08 April 2020.

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

In your comments on the draft decision, you requested an extension of the deadline to provide information from 30 to 60 months from the date of adoption of the decision.

You justify the extension by stating that "*that some testing should be conducted sequentially to reduce the overall number of animal tests to be conducted. It is our understanding that the deadline given in the draft decision has been set based on testing a single substance but does not consider that large consortium discussions and decisions can take some time, particularly in relation to testing strategies for a category. While the registrants are keen to adhere to the deadlines as stipulated in the final decision, they are concerned that the deadline is too short when considering that decisions can only be made, and tests contracted, after each phase of the strategy. Therefore, the registrants respectfully request the deadline to be extended to 60 months.*"

You also provided information from the CRO with detailed information on the timeline for the requested testing.

Although the deadline originally proposed in the draft decision already takes sequential testing into account for the Substance, it is not possible to take into account an adaptation rejected in this decision or proposed to be improved based on future data not currently available.

It is however demonstrated by the CRO that additional time is requested in this specific case. ECHA has therefore extended the deadline to 48 months.

In your comments you raised the issue of updating the registration tonnage band of one or more registrations. ECHA does not take into account new information on volumes or tonnage band after the date on which the draft decision is notified to the registrants according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation). Therefore, your comments on this matter do not impact the decision.

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.

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

Appendix D: List of references - ECHA Guidance[12] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[13]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[14]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[12] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[13] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

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

You must provide the information requested in this decision for all REACH Annexes applicable to you.

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]
[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.