~~Confidential~~

Helsinki, 25 March 2022

Addressees
Registrants of JS - 2-Octyldodecan-1-ol as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
11/07/2017

Registered substance subject to this decision ("the Substance")
Substance name: 2-octyldodecan-1-ol
EC number: 226-242-9

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 ***1 April 2025***.

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

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

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

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

1. Justification for an adaptation of a Screening for reproductive/developmental toxicity based on the results of the Extended one-generation reproductive toxicity study requested below (Annex VIII, Section 8.7.1.)

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

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

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

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

D. 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) in rats, oral route, 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:

- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

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 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 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.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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 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.

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

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided three short-term toxicity studies on aquatic invertebrates, with test duration of 48 hours ([redacted] 2010, [redacted] 1999, [redacted] 2002). The dossier contains an adaptation to the information requirement on long-term toxicity on aquatic invertebrates under Annex XI Section 2 and column 2 of Annex IX section 9.1.

- *Triggering of the information requirement*

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do 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 (ECHA Guidance R.7.8.5).

In the provided ASTM E 1148 ([redacted], 2009), the saturation concentration of the Substance in water was determined to be below the limit of detection of the analytical method (*i.e. <0.1 mg/L*).

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

- *Assessment of the information provided*

We have assessed the adaptation submitted in the dossier on long-term toxicity on aquatic invertebrates using Annex XI Section 2 and column 2 of Annex IX section 9.1. For the reasons explained under Appendix C.1, the information submitted is not considered compliant.

The selection of the requested test on long-term toxicity on aquatic invertebrates, the test design and your comments on the draft decision are addressed under Appendix C.1.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Justification for an adaptation of a Screening for reproductive/ developmental toxicity based on the results of the Extended one-generation reproductive toxicity study

Screening for reproductive/developmental toxicity is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

The present decision requests the registrants concerned to generate and submit an extended one-generation reproductive toxicity study (EOGRTS) (see Appendix D.2). Once an EOGRTS is available, according to Column 2 of Annex VIII, Section 8.7.1. and in order to prevent unnecessary animal testing, a screening for reproductive/developmental toxicity does not therefore need to be conducted. While you still have to comply with the information requirement in Annex VIII, Section 8.7.1., you are requested to submit a justification for the adaptation based on Column 2 of that provision.

2. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided four short-term toxicity studies on fish, with test duration of 48 or 96 hours ([redacted] 1986: [redacted] 1986 [redacted] 1997, [redacted] 2012) and an adaptation to the information requirement on long-term toxicity on fish using Annex XI Section 2 and column 2 of Annex IX section 9.1.

- *Triggering of the information requirement*

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 (ECHA Guidance R.7.8.5).

As already explained under Section A.1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

- *Assessment of the information provided*

We have assessed the adaptation submitted in the dossier on long-term toxicity on fish using Annex XI Section 2 and column 2 of Annex IX section 9.1. For the reasons explained under Appendix C.2, the adaptation submitted is not considered compliant.

The selection of the requested test on long-term toxicity on fish, the test design and your comments on the draft decision are addressed under section C.2.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

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

You have provided the following information:

i. a justification to omit the study which ECHA understands to be based on technical feasibility (Annex XI, Section 2),
ii. a justification to omit the study refering to Chemical Safety Assessment specified in Annex IX, Section 9.1 Column 2;
iii. You further argue that '*the low solubility and ready biodegradability means that it is unlikely that aquatic life will be exposed to C20 long chain alcohols over extended periods'*.

We have assessed this information and identified the following issues:

A. As stated in Annex XI, Section 2, testing for a specific endpoint may be omitted if it is technically not possible to conduct the study as a consequence of the properties of the substance. The guidance given in the test methods referred to in Article 13(3), more specifically on the technical limitations of a specific method, must always be respected. Any technical difficulties to perform the test and the proposed solutions must be clearly documented.

   Long-term toxicity testing on aquatic invertebrates must be performed in accordance with OECD TG 211. This OECD TG provides that technical limitations in the aquatic toxicity studies, which arise from limited solubility, must be avoided by following the guidance on difficult to test substances, OECD GD 23 (ENV/JM/MONO(2000)6/REV1).

   In your justification, you have claimed that the study is technically not feasible which you have supported with the following statement "*In a review of aquatic toxicity testing of sparingly soluble compound, Rufli et al., (1998) reported that significant uncertainty exists in indentifying the true exposure concentrations in toxicity tests due to the limited solubility of the substances in water. In addition, the interpretation of toxicity responses observed above the solubility limit is aggravated by artefacts and that testing should only occur at or below the limit*.". You conclude that "*The data requirement is waived because the study is not technically feasible*".

   However, you have referred to a review on aquatic toxicity testing on sparingly soluble compounds, but you have not clarified how the data relates to the Substance. Furthermore, you have not described and documented any intention to mitigate the problems with limited solubility and perform the study following the guidance on difficult to test substances according to the OECD GD 23.

   Therefore, you have not demonstrated that the study is technically not possible to conduct and your adaptation is rejected.

B. The Chemical Safety Assessment, Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

You refer to Chemical Safety Assessment in your adaptation and claim that no chronic aquatic toxicity is expected based on the OECD SIDS Initial Assessment Report for Long Chain Alcohols (2006).

However, the Chemical Safety Assessment cannot be used in any adaptation opportunity described in the REACH Regulation to omit information on long-term toxicity to aquatic invertebrates.

C. A registrant can only adapt this information requirements in accordance with the adapations set out in Annex XI.

You argue that the Substance and all Guerbet alcohols of chain lengths at least up to C32 are readily biodegradable. However, your justification to omit this information based on biodegradability does not refer to any legal basis under Annex XI to REACH.

Therefore, the provided arguments on degradation cannot be used in any adaptation opportunity described in the REACH Regulation to omit this information.

In the comments to the draft decision, you "*recognize and accept the rejection of the adaptation of the information requirements*" by ECHA. Rather than conducting the tests required in the decision, you consider that "*there should be an integrated testing strategy employed for the entire category to minimize vertebrate tests for animal welfare reasons and to avoid unnecessary animal tests with no additional value*".

You indicate your intention to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

You propose to predict the long-term toxicity on aquatic invertebrates and fish properties of the Substance from new studies on category members of 'Guerbet alcohols'.

You consider that "*aquatic toxicity is only observed up to the C14/C15 carbon range. Beyond that, the alcohols are too water insoluble to result in aquatic toxicity*". On this basis, rather than conducting the tests required in the decision, you propose "*If no toxicity is observed with 2-hexyldecan-1-ol, then no additional aquatic toxicity studies would be required and these studies can be read-across to the longer chain Guerbet alcohols (2-octyl-dodecan-1-ol, 2-decaltetradecanol)*".

You present a strategy relying on the generation of supporting information on some category members. More specifically you intend to first conduct aquatic chronic toxicity studies with Daphnia (OECD TG 211) and fish (OECD TG 210) on the category members 2-butyloctan-1-ol (CAS 3913-02-8) and 2-hexyldecan-1-ol (CAS 2425-77-6). You would subsequently decide, based on the results of these studies, on whether the read-across to the longer chain Guerbet alcohols (2-octyl-dodecan-1-ol, 2-decaltetradecanol) is supported or whether further testing of category members is needed.

ECHA acknowledges your intention to generate information on some category members and your plan to apply read-across approach. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, therefore no conclusion on the compliance can currently be made.

Please note that this decision does not consider 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 remain responsible for complying with this decision by the set deadline.

On this basis, your adaptations are rejected and the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to the low water solubility (<0.1 mg/L) and adsorptive properties (log kow 8.63). OECD TG 211 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 211. 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.

2. Long-term toxicity testing on fish

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

You have provided the following information:

i. a justification to omit the study which ECHA understands to be based on technical feasibility (Annex XI, Section 2),
ii. a justification to omit the study refering to Chemical Safety Assessment specified in Annex IX, Section 9.1 Column 2;
iii. You further argue that '*the low solubility and ready biodegradability means that it is unlikely that aquatic life will be exposed to C20 long chain alcohols over extended periods'*.

We have assessed this information and identified the following issues:

A. As stated in Annex XI, Section 2, testing for a specific endpoint may be omitted if it is technically not possible to conduct the study as a consequence of the properties of the substance. The guidance given in the test methods referred to in Article 13(3), more specifically on the technical limitations of a specific method, must always be respected. Any technical difficulties to perform the test and the proposed solutions must be clearly documented.

   Long-term toxicity testing on fish must be performed in accordance with OECD TG 210. This OECD TG provides that technical limitations in the aquatic toxicity studies, which arise from limited solubility, must be avoided by following the guidance on difficult to test substances, OECD GD 23 (ENV/JM/MONO(2000)6/REV1).

   In your justification, you have claimed that the study is technically not feasible which you have supported with the following statement "*one short-term fish study for long chain alcohols with limited duration (7 days) and related to 1-octanol exposure. Measured concentrations of 1-octanol declined more than 90% over the period of the test demonstrating that it is impractical to carry out long-term toxicity testing with sparingly soluble substances.*".

However, you have referred to a study with 1-octanol, but you have not provided this data in the dossier nor clarified how the data relates to the Substance.

Furthermore, you have not described and documented any intention to mitigate the problems with limited solubility and perform the study following the guidance on difficult to test substances according to the OECD GD 23.

Therefore, you have not demonstrated that the study is technically not possible to conduct and your adaptation is rejected.

B. The Chemical Safety Assessment, Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

   You refer to Chemical Safety Assessment in your adaptation and claim that no chronic aquatic toxicity is expected based on the OECD SIDS Initial Assessment Report for Long Chain Alcohols (2006).

   However, the Chemical Safety Assessment cannot be used to omit information on long-term toxicity to fish.

C. A registrant can only adapt this information requirements in accordance with the adapations set out in Annex XI.

   You argue that the Substance and all Guerbet alcohols of chain lengths at least up to C32 are readily biodegradable. However, your justification to omit this information based on biodegradability does not refer to any legal basis under Annex XI to REACH.

   Therefore, the provided arguments on degradation cannot be used in any adaptation opportunity described in the REACH Regulation to omit this information.

Your comments on the draft decision are common to another request in this decision and are jointly addressed under section C.1 above.

On this basis, your adaptations are rejected and the information requirement is not fulfilled.

Study design

The OECD TG 210 specifies that for difficult to test substances the 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 Appendix C.1.

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

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

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

You have provided a study similar to the OECD TG 414 in rabbit (Iglesias et al 2002 [1], key study) with the source substance docosan-1-ol, EC No. 211-546-6, CAS No. 661-19-8.

The study submitted is based on an adaptation under Annex XI, Section 1.5 (Grouping and read-across approach).

As explained in the Appendix on Reasons common to several requests Annex XI, Section 1.5. imposes two conditions whenever a read-across approach is used. Firstly, there needs to be structural similarity between the grouped substances. Secondly, the relevant properties of the Substance may be predicted from data for the reference substance.

You have provided a read-across justification document in [redacted] in IUCLID Section 13.2.

You predict the properties of the Substance from the structurally similar substance: docosan-1-ol, EC No. 211-546-6, (CAS No. 661-19-8 ; i.e. the source substance), a long chain linear alcohol.

The source study that you have used in your read-across approach, [Iglesias et al, 2002 [1], corresponds to a Prenatal Developmental Toxicity Study performed similar to the OECD TG 414.

You have provided the following reasoning for the prediction of toxicological properties: "*structural similarity (i.e. all substances under consideration being part of a homologous group) and similar properties between SIDS Long Chain Alcohols and Guerbet Alcohols categories", including the common functional group (alcohol group), "support consideration of these substances as structural analogues for the purpose of read-across*" and allows that *"the information from this [Long Chain Alcohol] category can be used for read-across of data for certain end points to Guerbet Alcohols".*

In particular, you state that "*Due to its structural similarity and the same toxicological pattern in studies of acute and repeated oral toxicity 1-Docosan-1-ol is an appropriate read-across substance for the Guerbet alcohols and the data of the developmental toxicity study in rabbbits can be read across*".

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.

ECHA has assessed this information and notes the following shortcomings with regards to the prediction of toxicological properties.

- *Supporting information to compare properties of of the substances*

As explained in the Appendix on Reasons common to several requests Annex XI, Section 1.5. states that it is important to provide supporting information to strengthen the read-across rationale in order to establish that the properties of the Substance can be predicted from the

data on the source substance(s). Relevant, reliable and adequate information is needed, for example from bridging studies of comparable design and duration, allowing to compare the properties of the Substance and of the source substance and confirm that both substances cause the same type of effects.

In particular it needs to be established that the source substance and the Substance cause the same type of effects despite the following structural differences identified between the source substance and the Substance: the source substance is linear with a carbon chain length of 22, the Substance has a carbon chain length of 12 and is branched at the C2 position.

In order to support your prediction you refer to the following information on the source substance: the developmental toxicity study used in the prediction as well as oral acute toxicity, and a sub-chronic toxicity (90-day) study provided in the registration dossier. You also refer to information from oral acute toxicity and sub-chronic toxicity (90-day) studies with the Substance in the dossier.

However, ECHA notes that acute and repeated dose toxicity studies do not inform on the developmental toxicity properties of the Substance and of the source substance. Accordingly, this information is not considered as relevant to support your hypothesis.

In addition, your read-across justification and the technical dossier do not include any other information of comparable design and duration for the Substance and source substance that allow to compare the developmental toxicity properties between these substances. This means that no information is provided to establish that the structural differences identified between these substances, i.e. the branching compared to the linear structure of the alcohols, as well as the chain length, do not impact the prediction for the toxicological properties under consideration.

Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and the source substance to support your read-across hypothesis.

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

Therefore, the information requirement is not fulfilled.

Information on study design

A PNDT study according to the OECD TG 414 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.

In the comments to the draft decision you agree with the request.

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 provided the following information under IUCLID section 7.8.1:

i. a study according to the ICH Harmonised Tripartite Guideline S5(R2) "Detection of toxicity to reproduction for medicinal products and toxicity to male fertility" (key study, Iglesias et al 2002 [2]) with the source substance docosan-1-ol, EC No. 211-546-6, CAS No. 661-19-8;
ii. a repeated dose toxicity study similar to OECD TG 408, assessing reproductive organs (supporting study, Iglesias et al 2002 [3]) with the source substance docosan-1-ol, EC No. 211-546-6, CAS No. 661-19-8; and
iii. a justification for data waiving: "*No Extended One-Generation Reproductive Toxicity Study is needed since: 1) A reliable one-generation study in rats is available; 2) No additional information is expected to be obtained from the second generation [Janer et al., Reprod. Toxicol. (2007), 24(1), 103-13]; 3) Repeated dose studies did not reveal any adverse effects on the gonads or other fertility effects; 4) No teratogenic effects were observed in a prenatal developmental toxicity study (OECD 414)*".

ECHA understands that you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2 of REACH (weight of evidence) and has evaluated the provided information accordingly. ECHA also understands that your weight of evidence adaptation is based on information from studies i. and ii. above and on the following studies provided under IUCLID sections 7.5.1 and 7.8.2:

iv. a study similar to OECD TG 408 ([redacted] 1973) with the Substance
v. a study according to OECD TG 414 in rat ([redacted] 1994) with the Substance.

Based on the presented sources of information, you argue that the available data gives sufficient information to conlude on the reproductive toxicity because you consider the provided study i. provides the necessary information and in addition no adverse teratogenic effects or adverse effects on gonads or fertility were observed in studies iv. and v. with the Substance.

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.

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 adaptation.

While you have identified the sources of information on which your adaption is based, you have not included a justification with an assessment, integration and weighing of the individual sources of information for relevance, reliability, coverage, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex IX/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.

1) Sexual function and fertility

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, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The source of information i. provides relevant information on mating, fertility, maintenance of pregnancy (abortions, total resorptions), organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis. The information sources ii. and iv. provide relevant information on organ weights and histopathology of reproductive organs and tissues. The source of information v. provides relevant information on maintenance of pregnancy (abortions, total resorptions).

However, the sources of information i. and ii. have the following deficiencies affecting their reliability.

- *Supporting information to compare properties of the substances (studies i. and ii.)*

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). 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(s).

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

In particular it needs to be established that the source substance and the Substance cause the same type of effects despite the following structural differences identified between the source substance and the Substance: the source substance is linear with a carbon chain length of 22, the Substance has a carbon chain length of 20 and is branched at the C2 position.

The studies i. and ii. were conducted with an analogue substance, a linear long chain alcohol: You predict the properties of the Substance from the structurally similar substance docosan-1-ol, i.e. the source substance. You have provided a read-across justification document in "Read Across Justification_Guerbet alcohols_Final4" in IUCLID Section 13.2.

You have provided the following reasoning for the prediction of toxicological properties: "*structural similarity (i.e. all substances under consideration being part of a homologous group) and similar properties between SIDS Long Chain Alcohols and Guerbet Alcohols categories", including the common functional group (alcohol group), "support consideration of these substances as structural analogues for the purpose of read-across*" and allows that *"the information from this [Long Chain Alcohol] category can be used for read-across of data for certain end points to Guerbet Alcohols".*

In particular, you state that "*Due to its structural similarity and the same toxicological pattern in studies of acute and repeated oral toxicity as well as in developmental studies 1-Docosan-1-ol is an appropriate read-across substance for the Guerbet alcohols and the data […] can be read-across to the whole category.*"

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.

In order to support your prediction you refer to the following information on the source substance: the reproductive toxicity study used in the prediction as well as oral acute toxicity, and sub-chronic toxicity (90-day) and developmental toxicity studies provided in the registration dossier. You also refer to information from an oral acute toxicity study, sub-chronic toxicity (90-day) and developmental toxicity studies with the Substance in the dossier.

However, ECHA notes that acute toxicity studies do not inform on the reproductive toxicity properties of the Substance and of the source substance. Repeated dose and developmental toxicity studies do not inform on effects on fertility, i.e. mating and reproductive function. Furthermore, the developmental toxicity study with the source substance was conducted in rabbit, the developmental toxicity study with the Substance in rat. These studies in different species cannot serve as bridging information to compare properties.

In addition, your read-across justification and the technical dossier do not include any other information of comparable design and duration for the Substance and source substance that allow to compare the reproductive toxicity properties between these substances and to show that the substances have similar properties covered by reproductive toxicity studies, i.e. sexual function and fertility and on toxicity to offspring. This means that no information is provided to establish that the structural differences identified between these substances, i.e. the branching compared to the linear structure of the alcohols, as well as the chain length, do not impact the prediction for the toxicological properties under consideration.

Therefore the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and the the source substance to support your read-across hypothesis.

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

Therefore, based on the information in the dossier, your read-across adaptation contains such significant deficiency that it cannot reliably contribute to your weight of evidence adaptation.

The sources of information iv. and v. provide relevant and reliable information on organ weights, histopathology of reproductive organs and tissues and on maintenance of pregnancy. In the absence of reliable information on mating, fertility, gestation (length), parturition,

lactation, nursing performance, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

2) Toxicity to the offspring

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

The sources of information i. and v. provide relevant information on toxicity to the offspring *in utero*. They inform on deaths before birth, skeletal and visceral malformations.
In the studies i. and v. the dams were sacrificed on gestation day 20, therefore the studies do not inform on postnatal investigations up to the adulthood.

The sources of information ii. and iv. do not provide relevant information on toxicity to the offspring at all.

The information provided on toxicity to offspring is limited and does not cover all relevant and essential aspects as defined above. Neither source of information informs on toxicity to the offspring up to adulthood.

The sources of information i. and v. provide relevant information on toxicity to the offspring before birth. However, the reliability of the contribution of the source of information i. to the weight of evidence is limited as explained in the section *1)* above, under *Supporting information to compare properties of the substances (studies i. and ii.)*.

Therefore, the only relevant and reliable information for systemic toxicity for the F1 generation is the source of information v. In the absence of reliable information on deaths during or after birth, clinical signs, sexual maturity, oestrous cyclicity, organ weights and histopathology of reproductive organs and tissues in adulthood, no conclusion can be drawn on toxicity to the offspring as required by the information requirement.

3) Systemic toxicity

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.

All sources of information provide relevant information on systemic toxicity in the parental P generation.

Sources of information ii. and iv. inform on systemic toxicity, especially haematology, clinical chemistry and organ weight and histopathology of non-reproductive organs from up to 20 adult animals/sex/group (source ii.). Source of information i. and v. include very limited investigations in dams, e.g. survival, body weight, gross pathology.

The sources of information i. and v. inform on toxicity to the fetus. However, none of the sources of information provide relevant information on systemic toxicity in the F1 generation up to adulthood.

The reliability of the contributions of the sources of information i. and ii. to the weight of evidence is limited as explained in the section *1)* above, under *Supporting information to*

compare properties of the substances (studies i. and ii.).

The sources of information iv. and v. provide relevant and reliable information for systemic toxicity for the P generation. However, as indicated above there is no information on systemic toxicity of the F1 generation up to adulthood. Due to lack of all of the relevant and reliable information on systemic toxicity in the F1 generation, it is not possible to conclude on that property.

Taken together, the sources of information as indicated above, provide information as described below:

- They provide information on organ weights and histopathology of reproductive organs and tissues and on maintenance of pregnancy (abortions, total resorptions). They provide information on sexual function and fertility on the parental P generation but the reliability of this information is affected by the critical deficiency of the read-across adaptation. However, the sources of information provide no reliable information on mating, fertility, gestation (length), parturition, lactation, nursing performance.
- They provide some information on toxicity to offspring, but this information does not cover relevant information on life stages of the F1 generation (postnatal period up to adulthood).
- They provide some information on Systemic toxicity, but this information does not cover relevant information on life stages of the F1 generation (postnatal up to adulthood.

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.

Consequently, 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.[2]

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.

[2] ECHA Guidance R.7a, Section R.7.6

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.

Species and route selection

The study must be performed in rats with oral[3] administration.

In the comments to the draft decision you agree with the request.

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 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 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 Guidance on IRs & CSA, Section R.7.6.

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

Appendix E: 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[4].

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[5].

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

Appendix F: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 05 January 2021.

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

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

Deadline to submit the requested information in this decision

In your comments on the draft decision, you requested an extension of the deadlines from 30 to 42 months from the date of adoption of the decision to provide the requested information.

You have provided three laboratory statements along with your comments in which you based your request for a deadline extension on your proposed tier-testing approach for mammalian studies (sub-chronic toxicity study, pre-natal developmental toxicity studies and extended-one generation reproductive toxicity study), starting with the completion of four OECD 422 studies. The statements from the 3 testing laboratories inform on the timelines required to conduct the four OECD 422 studies, as you are of the opinion that all four studies should be conducted in the same laboratory. You indicate that "*if a certain trend is observed within the group (e. g. decreasing toxicity with increasing C-chain length) it might be possible to avoid testing each single substance for all endpoints. Therefore, it is crucial that all OECD 422 studies will be finalized before any other study will be started. Consequently, the developmental toxicity study in rabbits (OECD 414) and the extended one generation study (OECD 443) which are requested by ECHA in this decision will have to be performed afterwards.*"

Furthermore, you motivated your request for a deadline extension also based on extra time needed for the aquatic toxicity testing. You point out that, in your experience, "*the performance of chronic aquatic toxicity studies of substances with very low water solubility is very time consuming due to the difficulty of analytical method development*". You further stress that "*laboratories with high proficiency in performing these sophisticated aquatic analyses are limited*", hinting at laboratory capacity challenges. To support your arguments, you have attached a statement from one testing laboratory outlining potential dates for delivery of a test report, taking into account the workload at the laboratory.

Development of the analytical method and laboratory capacity for aquatic toxicity testing

In your comments, you have indicated a need for development of analytical method and laboratory capacity challenges. ECHA acknowledges that extra time may be needed to develop a suitable analytical method and to accommodate for the laboratory capacity as per the attached statement. For the reasons you put forward, ECHA considers that 33 months are required to provide the requested data.

Intention to develop an adaptation

In your comments to this draft decision you expressed your agreement to conduct the requested studies on the Substance. You also expressed your intention to fulfil the information

requirements for the sub-chronic toxicity study and pre-natal developmental toxicity studies applicable to the category members 2-butyloctan-1-ol (EC 223-470-0), 2-hexyldecan-1-ol (EC 219-370-1) and 2-decyltetradecanol (EC 261-385-0) by other means than by generating the requested information, i.e. via a tier-testing approach with some category members. The information on the Substance requested in this decision, i.e. pre-natal developmental toxicity studies and EOGRTS, is one of the elements of this tier-testing approach, as described above.

The timeline set in this decision allows for generating the required data on the Substance. Therefore, for the purpose of complying with this decision, a further extension of the deadline set in this decision to accommodate the development of potential adaptations to fulfil information requirements applicable to other members of the category is not justified.

In conclusion, the deadline to submit the information requested in this decision is extended to 33 months from the date of the decision.

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 G: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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[9]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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 H: 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]

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.