~~Confidential~~

Helsinki, 06 September 2021

Addressee
Registrants of JS_FA 18:1 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
26/02/2016

Registered substance subject to this decision ("the Substance")
Substance name: (Z)-octadec-9-enol
EC number: 205-597-3
CAS number: 143-28-2

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 ***11 September 2024***.

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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

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

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

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

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 (rat or rabbit)

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 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, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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

1. Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

You seek to adapt the information requirements for the following standard information requirements by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach in general before assessing the specific standard information requirements in the following appendices.

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

In your registration dossier you have formed a group (category) of ''C6-24 Alcohols'. 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".* It is further specified that *'The majority of the category members have saturated alkyl chains'*.

[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

a. Prediction for toxicological 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:

In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Alcohols, C16-18 and C18-unsatd., EC 268-106-1, OECD 471, [redacted], 1989;

In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Docosan-1-ol, EC 211-546-6, similar to OECD 473, non-GLP, Iglesias, 2002

In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Docosan-1-ol, EC 211-546-6, similar to OECD 476, non-GLP, Iglesias, 2002

Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Hexadecan-1-ol, EC 253-149-0, non-TG/GLP, [redacted], 1966
- Hexan-1-ol, EC 203-852-3, non-TG/GLP, [redacted], 1966
- Hexadecan-1-ol, EC 253-149-0, OECD 407, [redacted], 1985

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Docosan-1-ol, EC 211-546-6, OECD 422, [redacted], 1992;
- Docosan-1-ol, EC 211-546-6, non-TG/GLP, Iglesias, 2002;
- C24-34 even chain alcohols, non-TG/GLP, Rodriguez, 1998;
- 3-methylbutan-1-ol, EC 204-633-5, OECD 414, non-GLP, Klimisch and Hellwig, 1995;

Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)
- Docosan-1-ol, EC 211-546-6, similar to OECD 414, non-GLP, Iglesias, 2002;
- 3-methylbutan-1-ol, EC 204-633-5, OECD 414, non-GLP, Klimisch and Hellwig, 1995;
- C24-34 even chain alcohols, No EC/CAS provided, non-TG/GLP, Rodriguez, 1998;

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

1) Hypothesis does not address unsaturation

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the

substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[4]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

ECHA interprets that your read-across hypothesis relies on structural similarity between category members as a sufficient basis for predicting the properties of the Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach it does not necessarily lead to predictable or similar human health properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the category members. In particular, your hypothesis does not address the impact that unsaturation in the target Substance may have on the prediction.

In your comments to the initial draft decision you provide new arguments to address the impact that unsaturation in the target Substance may have on the prediction for mammalian toxicity:

i. You refer to OECD toolbox QSAR profiles of the (unsaturated) Substance and the equivalent chain length saturated member of the category (1-octadecanol) in which both have essentially the same structural alert profile (i.e. an absence of alerts for either substance).

ii. You also state that the significance of unsaturation on toxicokinetics of alcohols are in line with those of the saturated long chain alcohols, based on a number of sources and metabolite profiling. ECHA notes the OECD QSAR toolbox gave 25 metabolites for octadecane-1-ol and 42 for the Substance.

iii. You also provide an argument of natural occurrence of unsaturation in fatty acids, which result in dietary exposure.

The information you have provided in your comments addresses the incompliances identified in this decision regarding the impact of unsaturation on the predicted properties. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

2) 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.*

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

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.[5] 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.

Furthermore in larger categories there may be breaks in trends which could affect the reliability of interpolation.[6] To confirm that there are no such breakpoints, adequate and reliable information needs to cover also substances within a range of homologous series.

You have provided an *in vitro* gene mutation study in bacteria in only four bacterial strains for a source substance from the category that is unsaturated. Similarly for *in vitro* cytogenicity and *in vitro* gene mutation in mammalian cells you have provided only one study each. Based on the studies you conclude that the test substance is negative for mutagenicity to bacteria under the conditons of the test.

You have also provided PNDT studies in a first and second species for one category member, and two source substances outside the category boundaries (3-methylbutan-1-ol, EC 204-633-5 and C24-34 even chain alcohols (EC not specified)) 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 first and second species across the category (see requests C.2 and D.1).

However, you have not demonstrated that this information from three studies (one from category and two from non-category members) is sufficient to address the uncertainties and to establish a trend across the category consisting of 33 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. Therefore, the information provided is not sufficient to conclude that toxicological/ecotoxicological properties are likely to follow a regular pattern.

In your comments to the draft decision you state that a testing strategy is under consideration, with Phase 1 consisting of (a) *in vitro* genetic toxicity testing to strengthen the category hypothesis that members are not mutagenic or clastogenic and (b) to perform a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) with the Substance in order to confirm the inclusion of the substance into the Category of C6-24 linear and essentially-linear aliphatic alcohols. Based on the results of Phase 1, futher testing may be needed in Phases 2 and 3. However, you note '*that these bridging proposals are still under consideration by all parties at the present time, therefore this does not constitute a decision yet on the part of registrants in the context of Implementing Regulation 1435/2020*.' Therefore, as it is not possible to derive reliable prediction of the properties of the members in the category, your comment does not address the deficiency identified in this draft decision.

C. 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

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.1.5.
[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.2.

adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2

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

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

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 a(n) 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 C22) are not expected to impair fertility is based on a weight of evidence approach using data from reproductive screening studies [C12 (dodecanol), C18 (octadecanol)], a fertility study [C22 (docosanol)], together with a lack of effect on the reproductive organs in repeat dose studies over the range of linear and essentially linear alcohols. In addition there have been no other treatment related effects reported in any of the other studies both using 1-octadecen-9-enol and other alcohols from the category. Based on this it is concluded that 1-octadecen-9-enol is not expected to impair fertility"* and for developmental toxicity: *"Based on the weight of evidence from other alcohols across the category and the combined repeat dose/reproductive/developmental study with octadecan-1-ol, ([redacted] 1992, rel; 2) it is concluded that (z)-octadecen-9-enol is unlikely to be a developmental toxicant in the absence of maternal toxicity".*

You have not included in your justification for your weight of evidence adaptation, adequate and reliable 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 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.

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.

However, for the reasons explained in section 1 above, your read across adaptation is rejected.

While the deficiency common to several information requirements is set out above, specific deficiencies affecting the reliability of the sources of information are also set out under the information requirement concerned in the Appendices below.

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

1. In vitro gene mutation study in bacteria

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

You have provided an adaptation according to Annex XI, Section 1.5 (Grouping of substances and read-across approach). In support of your adaptation, you provided the following study:

Information provided in the dossier:

i. *In vitro* gene mutation study in bacteria with the following strains, TA 98, TA 100, TA 1535, TA 1537, and TA 1538 which all gave negative results, [redacted], 1989.

Information provided in the comments on the draft decision:

In your comments on the draft decision you have identied a new additional study:

ii. [redacted] ([redacted], 2017), according to OECD TG 471 and under GLP in the following strains, TA 98, TA 100, TA 1535, TA 1537 and Escherichia coli strain WP2uvrA

We have assessed this information and identified the following issues:

1) *Invalid read- across adaptation*

For the reasons explained in the "Appendix on Reasons common to several requests", your adaptations according to Annex XI, Section 1.5 is rejected.

2) Non-conformity with the applicable test guideline

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471[7] (1997). Some of the key parameters of this test guideline include:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)
b) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.

However, the reported data for the study (i.) you have provided did not include:

a) The required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101); and
b) Information on whether the negative control with a number of revertant colonies per plate were inside the historical control range of the laboratory.

The information provided does not cover some of the key parameters required by OECD TG 471.

3) [redacted], 2017 study

In your comments, you stated that information on *in vitro* gene mutation in five bacterial strains is available and that you will provide this information in an update of your

[7] ECHA Guidance R.7a, Table R.7.7–2, p.557

registration dossier. The information in your comment is not sufficient for ECHA to make an assessment, because you did not provided a robust study summary in an updated dossier. 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.

Therefore, the information requirement is not fulfilled.

Study design

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

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

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

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

You have provided an adaptation according to Annex XI, Section 1.5 (Grouping of substances and read-across approach) together with the following studies:

Information provided in the dossier:

i. *In vitro* chromosomal aberration study, OECD 473, Iglesisas, 2002 with docosan-1-ol, EC 211-546-6;
ii. *In vivo* micronucleus study, OECD 474, Iglesias, 2002 with docosan-1-ol, EC 211-546-6;
iii. *In vivo* micronucleus study, OECD 474, Hachiya, 1982 with octadecan-1-ol, EC 204-017-6

You have also provided an adaptation under column 2 to Annex VIII, Section 8.4.2. In support of your adaptation you refer to the studies under ii. and iii. above.

Information provided in the comments on the draft decision:

In your comments on the draft decision you have identied a new additional study:

iv. [redacted] ([redacted], 2017), conducted according to OECD TG 487 and GLP

We have assessed this information and identified the following issues:

1) Invalid read- across adaptation

For the reasons explained in the "Appendix on Reasons common to several requests", your adaptations according to Annex XI, Section 1.5 is rejected for all the studies submitted.

2) Non-conformity with the applicable test guideline

To fulfil the information requirement, the study has to be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[8]. The key parameter(s) of these test guidelines include:

a) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 3 concentrations must be evaluated, in each test condition.
c) The response for the concurrent negative control must be inside the historical control range of the laboratory.
d) Data on the cytotoxicity and the frequency of cells with structural chromosomal

[8] ECHA Guidance R.7a, Table R.7.7–2, p.557

aberration(s) for the treated and control cultures must be reported.

However, the reported data for the study (i) you have provided did not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
b) the evaluation of at least 3 concentrations in each test condition.
c) a negative control with a response inside the historical control range of the laboratory.
d) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

The information provided for study (i) does not cover key parameter(s) required by OECD TG 473.

3) Incompliance with column 2 to Annex VIII, Section 8.4.2.

Moreover, under Section 8.4.2., Column 2, first indent, Annex VIII to REACH, the study may be omitted "if *adequate data from an in vivo cytogenicity test are available*". ECHA Guidance[9] clarifies that the *in vivo* study must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively[10].

For the data from an *in vivo* cytogenicity test to be considered adequate, the *in vivo* study you submitted has to meet the requirements of OECD TG 474, and the specifications/conditions of this test guideline include, among others:

a) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow (e.g. a reduction in the proportion of immature erythrocytes among total erythrocytes in the bone marrow or peripheral blood).
b) In order to provide a clear negative outcome, the data available must show that "*bone marrow exposure to the test Substance occurred*".

However, the reported data for the *in vivo* study (ii.) you submitted did not include:

a) a maximum studied dose that is a MTD or induces toxicity
b) a negative control with a response inside the historical control range of the laboratory.
c) a demonstration that the systemic or target tissue (bone marrow) exposure to the Substance or its metabolites.

The information provided for study (ii.) does not cover specifications of OECD TG 474. Therefore, the conditions of Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

4) [redacted], 2017 study

In your comments, you stated that information on *in vitro* micronucleus study is available and that you will provide this information in an updated of your registration dossier. The information in your comments is not sufficient for ECHA to make an

[9] ECHA Guidance R.7a, R.7.7.6.3, p.568
[10] ECHA Guidance R.7a, Table R.7.7–3, p.558

assessment, because you did not provide sufficient information equivalent to a robust study summary.

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

Therefore, the information requirement is not fulfilled.

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

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

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in section 1 of the Appendix on Reasons common to several requests.

If the result of the requested information in sections A 1. and B 1. in Appendices A and B is negative, the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 will be triggered.

ii. Assessment of information provided

You have provided an adaptation according to Annex XI, Section 1.5 (Grouping of substances and read-across approach). In support of your adaptation, you provided the following study:

i. An *in vitro* gene mutation study in mammalian cells similar to OECD 476, Iglesias, 2002 with docosan-1-ol, EC 211-546-6

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

1) *Invalid read- across adaptation*

For the reasons explained in the "Appendix on Reasons common to several requests", your adaptations according to Annex XI, Section 1.5 is rejected.

2) Non-conformity with the applicable test guideline

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490[11]. The key parameter(s) of these test guidelines include:

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

[11] ECHA Guidance R.7a, Table R.7.7–2, p.557

b) The response for the concurrent negative control must be inside the historical control range of the laboratory.

However, the reported data for the study you have provided do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
b) a negative control with a response inside the historical control range of the laboratory.

The information provided does not cover key parameters required by OECD TG 476/490.

Therefore, the information requirement is not fulfilled.

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

In your comments on the draft decision, you agreed to conduct the study the Substance.

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

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided an adaptation according to Annex XI, Section 1.5 (Grouping of substances and read-across approach). In support of your adaptation, you provided the following studies:

i. Sub-chronic repeated dose study, non-GL/GLP, [redacted], 1966, with the analogue hexadecan-1-ol (EC 253-149-0; CAS 36653-82-4, C16).
ii. Sub-chronic repeated dose study, non-GL/GLP, [redacted], 1966, with the analogue 1-hexanol (EC 203-852-3, CAS 111-27-3, C6).
iii. Short-term repeated dose study, OECD 407 and GLP, [redacted], 1985, with the analogue hexadecan-1-ol (EC 253-149-0; CAS 36653-82-4, C16).

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

1) *Invalid read- across adaptation*

For the reasons explained under the "Appendix on Reasons common to several requests", your adaptation according to Annex XI, Section 1.5 is rejected for the analogues hexadecan-1-ol (EC 253-149-0) and hexanol (EC 203-852-3).

2) Non-conformity with the applicable test guideline

In addition, to be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a Sub-chronic toxicity study (90 day) has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, clinical biochemistry from each animal, and neurobehavioural examination.

However, in the sub-chronic studies i. and ii. you have provided this information is missing.

Moreover the study iii. you have provided does not have the exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 days.

Therefore, the information provided does not cover key parameters required by OECD TG 408.

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

In your comments to the draft decision you acknowledge the need for strengthening the read-across justification and implementing a bridging strategy. You furthermore indicate your intention to perform an OECD TG 422 study with the substance. However, you must note that an OECD TG 422 study with the substance does not meet the requirements of OECD TG 408 study.

Outcome

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is a liquid of very low vapour pressure. Uses with industial, professional and

consumer spray application are reported in the chemical safety report. However, the reported concentrations are low (<10%).

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX 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:

i. Combined repeated dose with screening for reproductive/developmental toxicity study in rats (similar to OECD TG 422) with source substance *docosan-1-ol,* EC 211-546-6, [redacted], 1992.
ii. Prenatal Developmental Toxicity Study in rabbits (non-TG/GLP) on source substance *Docosan-1-ol*, EC 211-546-6, Iglesias, 2002.
iii. Prenatal Developmental Toxicity Study in rabbits (OECD TG 414/non GLP) on source substance *3-methylbutan-1-ol*, EC 204-633-5, Klimisch and Hellwig, 1995.
iv. Developmental Toxicity study in rabbits (non-TG/GLP) on source substance *C24-34 even chain alcohols*, Rodriguez, 1998.

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 one species for the Substance in a weight of evidence adaptation, the sources of informations must cover the key elements foreseen to be investigated in an OECD TG 414 study in one species. The following aspects of this guideline include: 1) prenatal developmental toxicity in one species, 2) maternal toxicity in one species, and 3) maintenance of pregnancy in one species.

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

1) Non-conformity with the applicable test guideline

The above information must be obtain by following the specifications of the OECD TG 414. The key parameters of the OECD TG 414 include having 20 female animals with implantation sites for each test and control group and an exposure duration from implantation to the day prior to scheduled caesarean section.

However, study (i.) had exposure during days 6-19 of gestation and the termination was on day 29 of gestation. Study (ii.) had exposure for 15 days prior to mating up to day 17 of gestation. Study (iii.) had exposure during gestation days 7 to 19 and only 15 pregnant femals per dose level. Study (iv.) had exposure for days 6-18 of gestation and only 16 pregnant animals in the low dose group and 17 in the mid dose group. Consequently, none of the studies cover the full exposure duration from implantation to the day prior to scheduled caesarean section and additionally some of the studies

lack the required 20 female animals with implantation sites for each test and control group.

Therefore, these studies do not fulfil the conditions as foreseen in OECD TG 414.

2) *Invalid read- across adaptation*

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, this deficiency affects significantly the reliability of studies (i) to (iv) in the weight-of-evidence adaptations according to Annex XI, Section 1.2.

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

ECHA takes note of your intention stated in your comments on the Draft Decision to conduct a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) with the substance to confirm inclusion of the substance to the category.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[12] administration of the Substance.

In your comments to the draft decision you acknowledge the deficiency of the weight of evidence adaptation. ECHA takes note of your intention to support the toxicity information requirements of the C6-C24 within the category context using a targeted testing approach. The targeted testing approach proposed in your comments to the initial draft decision is addressed in the *Appendix on reasons common to several requests.*

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

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.

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

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.

For the reasons explained on Section C.2 above, while the sources of information (i) to (iii) provide information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy in a second species, this information is affected by significant deficiencies that compromise their reliability for the justification of your weight-of evidence adaptation.

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 second species, depending on the species tested in the first PNDT study (request C.2in this decision).

The study shall be performed with oral[13] administration of the Substance.

In your comments to the draft decision you acknowledge the deficiency of the weight of evidence adaptation. ECHA takes note of your intention to support the toxicity information requirements of the C6-C24 within the category context using a targeted testing approach. The targeted testing approach proposed in your comments to the initial draft decision is addressed in the *Appendix on reasons common to several requests.*

[13] 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[14].

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[15].

[14] https://echa.europa.eu/practical-guides
[15] https://echa.europa.eu/manuals

Appendix F: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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.

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

> In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 60 months from the date of adoption of the decision.
>
> You justify the extension by stating 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 a CRO with detailed information on the timeline for the requested testing.
>
> Although, the deadline in the draft decision already takes sequential testing into account as required, and it also includes time for planning and coordination of the requested studies it is acknowledged that some additional time is needed.
>
> On this basis, ECHA has therefore extended the deadline to 33 months.

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

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

Appendix G: List of references - ECHA Guidance[16] 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)[17]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[18]

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[19]

[16] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[17] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[18] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[19] 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]

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.