~~Confidential~~

Helsinki, 14 March 2022

Addressees
Registrant(s) of Hydroxycitronellol CAS107-74-4 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
04/04/2018

Registered substance subject to this decision ("the Substance")
Substance name: 3,7-dimethyloctane-1,7-diol
EC number: 203-517-1

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 ***19 June 2023***.

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. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or OECD TG 490)

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

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

- Appendices entitled "Reasons to request information required under Annexes VII to VIII 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.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of 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. 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 a key study in your dossier:

i. *in vitro* gene mutation study in bacteria (1983) according to OECD TG 471, with the Susbtance, and with the following strains, TA 98, TA 100, TA 1535, TA 1537, and TA 1538, which all gave negative results.

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

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471[2] (1997). The key parameters of this test guideline includes:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)
b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 µl/plate.
c) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

The reported data for the study/ies you have provided did not include:

a) results for the appropriate 5 strains, that is including the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).
b) a maximum dose of 5 mg/plate or 5 µl/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. In your dossier, you indicate that the highest concentration tested was 3.6 mg/plate without information on precipitate or limiting cytotoxicity.
c) data on the number of revertant colonies per plate for the treated doses and the controls.

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

Therefore, the information requirement is not fulfilled.

In the comments to the initial draft decision, you agree to perform the requested study.

Study design

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

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

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 Section 8.4.2., Column 2, and provided the following supporting study in your dossier:

i. *In vivo* micronucleus test (1983) according to OECD TG 474 with the Substance.

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

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[3] 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[4].

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:

a) The study must include a minimum of three doses/groups of treated animals, as well as a negative control group and a positive control group.
b) Each group must have a minimum of 5 analysable animals (the test can be performed in either sex).
c) Intraperitoneal injection as route of administration is to be used only with specific scientific justification.

The reported data for the *in vivo* study/ies you submitted did not include:

a) the appropriate control groups since no positive control group was included in the study.
b) a minimum of 5 animals per group since only 4 animals per group were tested.
c) a specific scientific justification for using the intraperitoneal route.

The information provided does not cover specifications/conditions required by OECD TG 474.

Therefore, the requirements of Section 8.4.2., Column 2, first indent, Annex VIII to REACH are not met.

In the comments to the initial draft decision, you agree to perform the requested study.

Study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

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

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 an adaptation 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 or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in sections A.1 and B.1.

The result of the requests for information in sections A.1 and B.1 will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ii. Assessment of information provided

You have provided an adaptation acording to Section 8.4.3., Column 2 and provided the following supporting study in your dossier:

i. *In vivo* micronucleus test (1983) according to OECD TG 474 with the Substance.

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

Under Section 8.4.3., Column 2, Annex VIII to REACH, the study may be omitted if adequate data from a reliable *in vivo* mammalian gene mutation test are available. ECHA Guidance[5] clarifies that the *in vivo* study must be a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay (TGR), performed according to OECD TG 488. This test investigates gene mutations using reporter genes.

Study (i) investigates chromosomal aberrations and not gene mutation.

This test is not a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay. Therefore, the requirements of Section 8.4.3., Column 2, Annex VIII to REACH are not met.

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 the comments to the initial draft decision, you agree to perform the requested study.

Study design

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Screening for reproductive/developmental toxicity

[5] ECHA Guidance R.7a, R.7.7.6.3, p. 568

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

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2 of REACH (weight of evidence).

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

(i) a non guideline experimental study (acute oral toxicity study in rats, 1973), with the Substance;
(ii) an experimental study (short-term oral repeated dose toxicity study, 2018) according to OECD TG 407, with the Substance;
(iii) QSAR predictions from the Danish (Q)SAR Database.

In your comments to the initial draft decision, you provide an additional source of information:

(iv) OECD SIDS Initial Assessment Report on the analogue substance Citral (EC No. 226-394-6, CAS No. 5392-40-5) (2001).

Based on the sources of information presented in the dossier, you argue that the available data gives sufficient information to conlude on reproductive/developmental toxicity because: *"The acute oral toxicity of the test item is very low (LD50: > 5 mL/kg). Also in a study with repeated oral dosing over 28 consecutive days no adverse clinical effects or histopathological findings were seen in rats dosed with up to 1000 mg/kg (NOAEL: > 1000 mg/kg). As also reported in the attached (Q)SAR predicted profile, the test item does not suggest a specific alert for a teratogenic potential in humans. Therefore, at present there is no need to perform a screening study for reproductive/developmental toxicity in experimental animals.".*

In your comments to the draft decision, you further claim that the source of information (iv) supports this conclusion. You consider that the use of results from the analogue substance Citral is justified because *"The analogy results in particular from the metabolism of citral, which is hydrogenated to alcohol in the organism"*.

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 listed various studies tackling some reproductive toxicity parameters to justify your adaptation, 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 VIII includes similar information that is produced by the OECD TG 421 or OECD TG 422. OECD TGs 421/422 require to investigate the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

1. Sexual function and fertility

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

The source of information (ii) only provides relevant information on organ weights and histopathology of reproductive organs. In your comments to the draft decision, you provide additional details on the histopathological results of study (ii) and indicate your intention to add them to your dossier. You further claim that the Substance is unlikely to affect sexual function and fertility because no changes were observed in the reproductive organs of treated animals compared to the controls.

However, information provided on sexual function and fertility is limited and does not cover all relevant and essential aspects as defined above.

The source of information (ii) does not inform on mating and functional fertility as required in OECD TG 421 or 422.

The source of information (iv) may provide relevant information on sexual function and fertility, but has the following deficiencies affecting its reliability.

You have adapted this information requirement by using a Grouping of substances and read-across approach and provided the source of information (iv), which refers in particular to results from an OECD TG 421 study and a non-guideline inhalation teratogenicity study with the analogue substance Citral (EC No. 226-394-6, CAS No. 5392-40-5).

You have not provided a read-across justification document with your comments to the draft decision but you provide the following reasoning for the prediction of this information requirement: *"To support this conclusion, the published results (OECD SIDS. CITRAL. UNEP PUBLICATIONS. SIDS Initial Assessment Report for 13th SIAM. (Switzerland, November 6-9, 2001).) of the tests on reproductive and developmental toxicity with the analogous substance citral can be used. It was concluded that the NOAELs for reproductive and developmental toxicity were established at 1,000 and 200 mg / kg / day, respectively. In an inhalation teratogenicity study, no developmental toxicity was observed even at the highest dose level of 68 ppm (423 mg / m3) (equivalent to 77 mg / kg / day). (See attachment) The analogy results in particular from the metabolism of citral, which is hydrogenated to alcohol in the organism".*

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.

We have assessed this information and identified the following issues:

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

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

We have identified the following issues with the prediction of toxicological properties:

Inadequate read-across hypothesis

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

Your read-across hypothesis is only based on the structural similarity between the source substance and the Substance, which you consider a sufficient basis for predicting the properties of the Substance. In particular, you assume that the source substance will be hydrogenated to an alcohol *in vivo.*

However, your hypothesis does not explain why the structural differences between the substances do not influence the toxicological properties or do so in a regular pattern. You also have not provided any information about neither the rate and extent of biotransformation of the source substance, nor on the actual metabolites produced. You have not provided information that would explain the structural differences between the substances and their impact on the prediction.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar toxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances.

Missing supporting information

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).

Supporting information must include information relevant to the endpoint to compare properties of the Substance and source substance to confirm your claimed prediction.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). 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).

For the source substance, you have provided the source of information (iv), which refers in particular to results from an OECD TG 421 study and a non-guideline inhalation teratogenicity study with the analogue substance Citral (EC No. 226-394-6, CAS No. 5392-40-5). You have not provided robust study summaries of these source studies. However, for the Substance, neither your read-across justification nor the registration dossier includes any information for comparison to confirm that both substances cause the same type of effects regarding reproductive and developmental toxicity.

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

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. Therefore, your read-across approach under Annex XI, Section 1.5. is rejected and and the source of information (iv) cannot contribute to the conclusion on sexual function and fertility.

Therefore, because essential key investigations are missing, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

2. Toxicity to offspring

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

In your comments to the draft decision, you claim that the Substance is unlikely to affect reproduction / development because no changes were observed in the reproductive organs of treated animals compared to the controls in study (ii). However, the source of information (ii) only investigates adult animals and does not provide any information on toxicity to offspring.

The source of information (iv) may provide relevant information on toxicity to offspring. However, the reliability of this source of information is significantly affected by the deficiencies identified and explained in the previous section, and it cannot contribute to the conclusion on toxicity to offspring.

The source of information (iii) only provides relevant information on developmental toxicity, but has the following deficiencies affecting its reliability.

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

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

With regard to these conditions, we have identified the following issue(s):

Modelled endpoint not well defined

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

- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes toxicity to offspring as investigated in an OECD TG 421/422 study.

You specify that the effect that is modelled is teratogenicity.

You have provided a (Q)SAR model, Danish QSAR Database which is based on data generated using different methodologies but which are not identified or described in your dossier.

Without this information, it is not clear and it cannot be excluded that the endpoint predicted by the (Q)SAR is not the same as the endpoint measured by the relevant test protocol.

In addition, the models included in the Danish QSAR Database for this endpoint are categorical models and thus do not provide quantitative information about effect levels (NO(A)EL, LO(A)EL), which are measured by the experimental study.

Therefore the endpoint of the model is not well defined and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

The prediction is not adequate due to low reliability

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

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

In addition, when several models are used, the results from multiple models for the same endpoint must be in agreement in order to ensure the necessary level of reliability.

Your registration dossier provides the following information:

- Developmental toxicity predictions using three different individual models: Leadscope, SciQSAR and CASE Ultra.
- A negative consensus prediction (Battery model) based on the majority of negative predictions from the above three models.
- Two negative predictions are obtained from Leadscope and CASE Ultra whereas one

positive prediction is obtained from SciQSAR.
- No justification provided for these different predictions.

The predictions for the Substance are not reliable because, the results from the individual models are not in agreement.

Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

Inadequate documentation of the model (QMRF)

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:
- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

You have not provided information about the model and its scientific validity.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

Lack of or inadequate documentation of the prediction (QPRF)

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:
- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You have not provided information about the prediction. Only the final result from the Danish QSAR Database is reported, without any information on e.g. analogues in the training set or how the applicability of the model is assessed for each substance.

In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

Overall, in the absence of reliable information on developmental toxicity, no conclusion can be drawn toxicity to offspring, as required by the information requirement.

3. Systemic toxicity

Relevant information must cover information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

The sources of information (i) and (ii) only provide relevant information on systemic toxicity (for P0 generation). Information provided on systemic toxicity is limited and does not cover all relevant and essential aspects as defined above.

The sources of information (i) and (ii) do not inform on systemic toxicity in F1 generation as required in OECD TG 421 or OECD TG 422.

The source of information (iv) provides relevant information on systemic toxicity in P0 and F1 generations. However, the reliability of this source of information is significantly affected by the deficiencies identified and explained in the previous sections. Although the available data allow a comparison of the subacute systemic toxicity in adult animals between the source and target substances, no data on systemic toxicity in pregnant animals, which might differ from that in unmated animals, and in offspring are available with the Substance. Therefore, similarity of systemic toxicity properties between the source and target substances is not sufficiently demonstrated and the source of information (iv) can only partly contribute to the conclusion on systemic toxicity.

Therefore, because essential key investigations on the Substance are missing, no conclusion can be drawn on systemic toxicity as required by the information requirement.

4. Conclusion

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

- Sexual function and fertility on parental P0 generation: weight and histopathology of reproductive organs, but lacking information on functional fertility (mating, fertility, gestation (length), parturition and lactation.
- Toxicity to offspring, but reliability of this information is significantly affected by the uncertain validity of the (Q)SAR model.
- Systemic toxicity, but not covering relevant information on life stages of the F1 generation up to postnatal day 13.

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.

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 421 or 422 study.

In your comments to the draft decision, you further refer to animal welfare considerations. However, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under Column 2 nor under the general rules of Annex XI.

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

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

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[6] administration of the Substance.

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

Appendix C: 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[7].

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[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

Appendix D: 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 14 December 2020.

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

ECHA took into account your comments and did not amend the requests or the deadline.

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

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

Appendix E: List of references - ECHA Guidance[9] 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)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

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[12]

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

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.