~~Confidential~~

Helsinki, 06 September 2021

Addressees
Registrant(s) of JS_71-23-8 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
06/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Propan-1-ol
EC number: 200-746-9
CAS number: 71-23-8

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 in A.1 and A.2 below by ***12 December 2022*** and all other information listed below by ***11 June 2024***.

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

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

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

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

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

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

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:

   - At least ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity); and
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

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

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

- "Reasons common to several requests";
- "Reasons to request information required under Annexes IX 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 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". 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: Reasons common to several requests

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

In your comments on the draft decision you seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

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

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

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. 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. Predictions for toxicological properties

You have provided a read-across justification with your comments. Relevant source studies are however not yet included in your dossier as discussed below. For that reason this assessment will focus on general principles of the read-across.

You read-across between the structurally similar substances, propyl acetate, EC no. 203-686-1 as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"the fast hydrolysis of n-propyl acetate to propan-1-ol and the fact that the blood levels from n-propyl acetate dosing are even higher than direct dosing of propan-1-ol".*

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regard to prediction of toxicological properties.

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

[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

- be adequate for the purpose of classification and labelling and/or risk assessment.

In order to be considered compliant and enable assessing if the Substance is a reproductive toxicant, the study has to meet the requirements of the respective guideline. More specifically, according to OECD TG 414, paragraph 14, "…*the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering.* Similarly, according to OECD TG 443, paragraph 21 "*If the dose levels are based on toxicity, the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals*."

For OECD TG 443 studies ECHA also specifies that dose level setting shall aim to induce systemic toxicity at the highest dose level.

The provisions relevant to exposure levels described above applies to your Substance if studies using a precursor are performed and your Substance is a metabolite of that precursor. This is because testing on a precursor may not reach the same level of exposure to the Substance as if the Substance was tested directly and thus may underestimate the toxicity of the Substance itself.

Therefore, the use of such study in a read-across adaptation must consider whether and to what extent the dose levels of the study based on toxicity of a precursor allows for the results to be appropriate for the purpose of classification and labelling and/or risk assessment for the substance.

There are at present no robust study summaries for studies with the proposed source substance propyl acetate in your registration dossier.

However, in your comments on the draft decision you have provided information relevant to predict exposure levels of the Substance in studies performed with the source substance, which can be regarded as a precursor of the Substance. You indicate based on a publication by [redacted] (2020) that *"Furthermore, consistent with measured in-vitro and in- vivo data, a recently published optimized propyl series PBPK model predicts rapid clearance of propyl acetate leading to higher concentrations of propanol in blood from propyl acetate inhalation compared to propanol inhalation in rats but not in humans, i.e. propyl acetate can be seen as a worst case read-across substance in the rat for this endpoint ([redacted] 2020)."*

[redacted], 2020 concludes in their publication that *"We developed a PBPK model for the propyl metabolic series in rats and humans for application to risk assessment. The model predicts rapid clearance of propyl acetate, higher levels of propanol from propyl acetate inhalation compared to propanol inhalation in rats but not humans,…."* However, the conclusion is not supported by data from figures 8 and 9 of the publication. Both figures show experimental data which demonstrates that, in rats:

- 86 µM air concentration of propanol lead to ~145 µM peak concentration of propanol in blood.
- 81.5 µM air concentration of propyl acetate lead to ~120 µM peak concentration of propanol in blood.

Adjusted for the difference in air concentration, the blood peak concentration of propanol should be 126 µM, whereas instead it is 145 µM following inhalation to propanol itself. Therefore, the experimental data does not support the conclusion of the authors, since propanol peak concentration in blood is highest after inhalation exposure to propanol and not propyl acetate.

Therefore, you have not demonstrated that the information in the source studies is adequate for the purpose of classification and labelling and/or risk assessment for propanol, because you have not demonstrated that the dose level setting for propanol aimed to induce systemic toxicity at the highest dose level is appropriate the Substance.

As a separate issue, it is noted that information on blood levels of source and target substances in your comments all stems from studies using inhalation exposure. In case studies relevant to this decision apply oral exposure expected exposure levels may then need to be justified using additional data, which you have not done and thus you have not demonstrated that the information is adequate for the purpose of classification and labelling and/or risk assessment.

Conclusions on the read-across approach

As explained above, source studies are at present not available, and you have not demonstrated that the exposure levels of those studies are in accordance with the respective OECD test guidelines. Therefore you have not yet established that relevant properties of the Substance can be predicted from data on the analogue substance. Your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

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

1. Long-term toxicity testing on aquatic invertebrates

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

You have adapted this standard information requirement 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:

A. QSAR prediction (OECD QSAR Toolbox v4.2; trend analysis with category members) of long-term toxicity to Daphnia, indicating the basis of effects as "reproduction",
B. Results of experimental study with analogue substance (propan-2-ol, EC No. 200-661-7): Daphnia magna Reproduction Test (OECD 211), [redacted] 1997.

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on long-term toxicity to aquatic invertebrates.

We have assessed this information and identified the following issues:

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular hazardous property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, 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.

ECHA has assessed the validity of your adaptation and identified the following issues:

To fulfil the information requirement, normally a study according to OECD TG 211 must be provided. The key investigations of this test are the concentrations of the test material leading to no observed effect (NOECs) estimated on the following parameters:

i) the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test,
ii) the survival of the parent animals during the test, and
iii) the time to production of the first brood.

i) Reproductive output

Both sources of information (A. and B.) provide the 21-day NOEC for reproduction as a basis for the effect but no other information, including the number of living offspring. Therefore, the provided information would only partially contribute to the key investigation.

The reliability of both sources of information is also significantly affected by the following deficiencies:

A Reliability of the QSAR information

Annex XI, Section 1.3 states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

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

I. 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.

The available QMRF provides profiling information and data only for 10 chemicals from the training set out of 43 data points. Furthermore, you have not provided the information on experimental protocol and data quality for the dataset used to develop the model. Data matrix report at the end of the QMRF document refers to a separate spreadsheet which is not provided.

QMRF provides profiling information and data for only 10 chemicals from the training set, therefore we cannot be certain on what type of data was used in the model. Furthermore, the connection between the analogues proposed in a category report and the number of data points (n=43) given in the prediction report is not clear. However, you have not provided the data matrix. In the absence of such documentation ECHA cannot trace the source and verify the quality of the individual data points. Therefore, it is not possible to exclude that other estimated data points were used instead/in addition to experimental data.

In absence of such information, ECHA cannot establish that the prediction is reliable for use in a weight of evidence adaptation.

II. 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,
- reliable input parameters are used,
- the prediction must be reliable based on the representativeness (and homogeneity) of

the elements in the training set.

In Section 1.1 of your technical dossier, you identify the Substance as propan-1-ol (EC: 200-746-9, CAS: 71-23-8).

For the assessment, you provided predictions for the following structures: aryl alcohol, cycloalkane, dihydroxyl derivatives, branched alkane with tertiary carbon, aryl, isopropyl, alkyl (hetero)arenes, alkyl-, alkenyl- and alkynyl-(hetero)arenes, ketone, ether.

With regard to structural similarity (similarity index) you have reported that five analogues have zero similarity to the target and the other four have similarity of 14%, 17% and 44%.

You have considered aryl alcohol, cycloalkane, dihydroxyl derivatives, branched alkane with tertiary carbon, aryl, isopropyl, alkyl (hetero)arenes, alkyl-, alkenyl- and alkynyl-(hetero)arenes, ketone, ether_as representative structures, similar to your Substance. However, you failed to justify your selection.

You have reported the 95% confidence interval for the predicted NOEC ranging from 3.73 to 1250 mg/L.

Based on the information provided, the similarity of the structures in the training set to your Substance is not established. The target substance (propan-1-ol) is a linear alcohol while the analogues in the training set have all the following functional groups or meaningful fragments: aryl alcohol, cycloalkane, dihydroxyl derivatives, branched alkane with tertiary carbon, aryl, isopropyl, alkyl (hetero)arenes, alkyl, alkenyl- and alkynyl-(hetero)arenes, ketone, ether. The differences between the organic functional groups are also observed according to the "[redacted]" schema and "[redacted]" schema provided in your category report. In addition, based on the similarity index proofs no sufficient structural similarity is possible to consider the selected chemicals as "category members" on a basis of structural similarity.

Furthermore, the training set is heterogeneous, significantly affecting their representativeness for the Substance you aim to predict. The heterogeneity of the training set increases the uncertainty of the prediction which is also reflected by the large confidence interval reported in the QPRF (95% for the predicted NOEC ranging from 3.73 to 1250 mg/L). Therefore, the information available does not establish that your training set is representative and homogeneous. Based on that you have not established that the model is applicable to your Substance with the necessary level of reliability.

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

B Reliability of the read across approach

You have provided the following information:

- Results of experimental study with analogue substance (propan-2-ol, EC No. 200-661-7): Daphnia magna Reproduction Test (OECD 211), [redacted], 1997.

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

According to Annex XI, Section 1.5., two conditions must be necessarily fulfilled to apply grouping and read-across. 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).

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance and read across related documents [4, 5].

With regard to the above conditions, we have identified the following issues:

I. Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).

You have provided studies conducted with other substance than your Substance in order to comply with the REACH information requirements and merely indicated that the study is on "structurally similar propan-2-ol". You have not provided documentation as to why this information is relevant for your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance.

II. Characterisation of the source substance

Annex XI, Section 1.5 of the REACH Regulation provides that "substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as group."

According to the ECHA Guidance, "the purity and impurity profiles of the substance and the structural analogue need to be assessed", and "the extent to which differences in the purity and impurities are likely to influence the overall toxicity needs to be addressed, and where technically possible, excluded". The purity profile and composition can influence the overall toxicity/properties of the Substance and of the source substance(s).[6] Therefore, qualitative and quantitative information on the compositions of the Substance and of the source substance(s) should be provided to allow assessment whether the attempted predictions are compromised by the composition and/or impurities.

You have not provided any information on the composition of the selected analogue substance (propan-2-ol), including its purity profile (typical concentration and concentration range of the main constituent) and the presence of impurities (their typical concentrations and concentration ranges).

Therefore, ECHA considers that it is not possible to assess whether the attempted prediction is compromised by the composition of the source substance.

III. Adequacy and reliability of supporting information

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, May 2008, ECHA.
[5] Read-across Assessment Framework (RAAF) March 2017, ECHA.
[6] Section R.6.2.3.1 of Chapter R.6: QSARs and grouping of Chemicals

a. No adequate and reliable coverage of key parameters

Annex XI, Section 1.5 requires that whenever read-across is used, there must be adequate and reliable coverage of the key parameters of the corresponding test methods, in this case OECD TG 211. On that basis, the following specifications apply:

- the percentage of mortality of the parent animals (female *Daphnia*) is ≤ 20% at the end of the test;
- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
- water quality monitoring within the test vessels (*i.e.* pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported;

You have provided a reference to an OECD 211 TG experimental study for propan-2-ol. However, you have not provided any information on the above specifications.

In the absence of such information, you have not demonstrated adequate and reliable coverage of the key parameters of the OECD TG 211.

b. Absence of confirmation

Annex XI, Section 1.5 requires that whenever read-across is used, there must be adequate and reliable documentation.

Furthermore, the link provided under data source section of your technical dossier refers to a summary table with the results of ecotoxicity tests of various chemicals conducted by the [redacted]. The following disclaimers are added to this table:

1) *"These tests are conducted based on OECD-GLP standard and OECD test guidelines. However, because most of these data have not been evaluated by experts, confirmation of test results is needed if these data are used for assessment."*
2) *"Tests conducted before FY 2002 needs confirmation of test results, because some of these tests were conducted using a dispersant".*

You have not provided any confirmation of the test results that would allow further assessment of the study.

Therefore, you have not provided adequate and reliable documentation.

ii) and iii) Survival of the parent animals during the test, and the time to production of the first brood

You have not provided any relevant information to cover these two key investigations.

C Conclusion on the weight of evidence approach

Taken together, both sources of information (A. and B.) provide only partially information on one key investigation i): the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test, and not on the other two: ii) the survival of the parent animals during the test, and iii): the time to production of the first brood.

Furthermore, the reliability of both sources is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

Therefore, it is not possible to conclude, based on any source of information alone or

considered together, whether your Substance has or has not the particular hazardous property foreseen to be investigated by OECD TG 211 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2. Long-term toxicity testing on fish

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

You have provided the following information:

(i) an adaptation which you consider to be based on Annex IX, Section 9.1, Column 2;
(ii) a reference to an OECD TG 204 study on a read-across substance: A prolonged toxicity test to *Oryzias latipes* conducted with 2-Propanol (performed according to OECD guideline 204 under GLP conditions with 14 days test duration), [redacted], 2007

We have assessed this information and identified the following issues:

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

Your adaptation under Annex IX, Section 9.1, Column 2 is therefore rejected.

(ii).
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 ECHA Guidance R.6 and related documents.

You have provided no read-across justification document.

You predict the properties of the Substance from the structurally similar substance: 2-Propanol, EC No. 200-661-7 (CAS No. 67-63-0; i.e. the source substance).

You have provided the following reasoning for the prediction of eco-toxicological properties:

"(…) *A prolonged toxicity test to fish conducted with 2-Propanol (performed according to OECD guideline 204 under GLP conditions with 14 days test duration), revealed as well no effects at 100 mg/l (NOEC > 100 mg/l)*".

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.

ECHA notes the following shortcomings with regards to the predictions of eco-toxicological properties.

Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including, among others, robust study summary(ies) of the source study(ies).[7]

A robust study summary must cover sufficient information to make an independent assessment of the study.[8]

In order to comply requirements you have only provided a NOEC value of the source substance (NOEC > 100 mg/L) and a reference to a study conducted with the source substance. You have not provided a robust study summary of the with the REACH information source substance.

In the absence of such documentation, ECHA cannot verify that the results to be read-across meet the criteria above.

Adequacy and reliability of the source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);

- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The source study that you refer to in your read-across approach is performed according to OECD TG 204 with species *Oryzias latipes* and has duration of 14 days.

- Adequacy and reliability of the applied method

Under Article 13(3), the following test methods can fulfil the standard information requirement of Annex IX, Section 9.1.6. for long-term toxicity testing on fish: fish early-life stage (FELS) toxicity test (Annex IX, Section 9.1.6.1.), fish short-term toxicity test on embryo and sac-fry stages (Annex IX, Section 9.1.6.2.) and fish juvenile growth test (Annex IX, Section 9.1.6.3.). Further, key parameters for a long-term test include, among others, observations on the stage of embryonic development, hatching and survival, abnormal appearance/behaviour, weight and length.

You have submitted a study under OECD test guideline 204.

OECD TG 204 was in fact a prolonged acute study with fish mortality as the major endpoint examined.

This test method is not part of those recommended to fulfil the standard information requirement.

[7] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

[8] How to report robust study summaries Practical Guide 3, version 2.0 – November 2012

Based on the description of the OECD TG 204, OECD TG 204 does not provide an adequate coverage of the above key parameters.

Furthermore, this test guideline is no longer applicable. It was deleted in 2014 following a decision from the OECD Council.

- Exposure duration

For species *Oryzias latipes*, the recommended duration for a long-term test, e.g. in OECD 210, is 30 days post-hatch.

The study has a duration of 14 days, using the species *Oryzias latipes*.

This is shorter than the exposure period expected for a long-term toxicity study on that fish species.

Therefore, the study you have provided does not meet the above requirements.

Your adaptation is therefore rejected and the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

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

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

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

You have provided a PNDT study in a first species and the following justification for an adaptation of the PNDT study in a second species: *"The study does not need to be conducted on second species based on the outcome of the first test and all other relevant available data on toxicity to reproduction." "In the one study of adequate reliability on developmental toxicity according to OECD guideline 414 the NOAEC for developmental toxicity was 8730 mg/m³ air (LOAEC: 17460 mg/m³) in rats (Nelson, 1988). Converted to an oral uptake, the NOAEC corresponds to approximately 2175 mg/kg bw/day and the LOAEC to approximately 4350 mg/kg bw/day, thus exceeding the limit dose concentration for developmental toxicity testing (1000 mg/kg) by far. Therefore, it is considered that a developmental toxicity study in a second species is not necessary for the sake of animal welfare."*

ECHA understands that you refer to an adaptation of Annex IX, Section 8.7.2., Column 2,

In your comment you propose to adapt this information requirement according to Annex XI, Section 1.5., using a source study with the analogue substance propyl acetate (EC no. 203-686-1).

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

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

A pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply, taking into account the results of the test in the first species or any other relevant avalable information.

You have not demonstrated that the results of test in the first species or any other relevant available information enable adaptations in accordance with Section 8.7 of Annex X or Annex XI.

As explained in the Appendix "Reasons common to several requests" your adaptation according to Annex XI, Section 1.5 is currently rejected.

Thus, your adaptations are rejected and the information requirement is not fulfilled.

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

The study must be performed with oral[9] administration of the Substance.

2. Extended one-generation reproductive toxicity study

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

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

You have provided a key study (i) according to OECD TG 413 (2004) with sperm parameter measurements and stated that: "*The study performed according to OECD 413 guideline requirements is considered to address the endpoint reproductive toxicity*.".

Furthermore, as supporting information, you have provided information from publications:

ii)"*Comparison of Behavioral Teratogenic Effects of Ethanol an N-Propanol administered by Inhalation to Rats"*, (Nelson B.K., Brightwell W.S., Burg J.R; 1985)
iii) "*Behavioral Teratology Investigation of 1-Propanol Administered by Inhalation to Rats"*, (Nelson B.K *et al*, 1989)
iv)"*Circulating Steroids in Male Rats Following Inhalation of n-Alcohol*" (Cameron *et al*, 1985) on sex hormone measurement.

In your comments you provided further (confidential) details on the information in the OECD TG 413 study from 2004, in particular related to organ weights.

You also proposed to adapt this information requirement according to Annex XI, Section 1.5., using a source study with the analogue substance propyl acetate (EC no. 203-686-1).

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

(i). Key study

To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH.
The criteria of this test guideline include:

- Investigation of effects on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood

The provided key study (i) does not provide the above investigation and the corresponding information is missing.

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

(ii). Supporting information

To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH. The criteria of this test guideline include:

- testing of at least three dose levels and a concurrent control
- at least 20 pregnant females per dose group in parental P0 generation),
- dosing of the Substance from should cover full spermatogenesis and folliculogenesis, mating, gestation, lactation, and exposure of the F1 generation up to the adulthood
- examination of relevant life stages
- examination of key parameters for sexual function and fertility

The supporting information (ii, iii) you have provided was conducted with two dose levels. The other information (iv) you have provided was conducted with one dose level only. Therefore it does not fulfil the criterion of at least three dose levels set in OECD TG 443.

The supporting information (ii, iii) you have provided was conducted with 15 pregnant females for each test group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of at least 20 pregnant females for each test group in P0 generation set in OECD TG 443. The other information (iv) included male rats only.

In the supporting information (ii, iii) you have provided, the first experiment exposed only male animals for 42 days before mating as the females were untreated. In the second experiment, both males and females were untreated before mating. The other information (iv) included male rats only, no mating in the study. As specified in ECHA Guidance, the premating exposure should cover full spermatogenesis and folliculogenesis, and therefore ten weeks premating exposure duration is required.

In the supporting information (ii, iii) you have provided, the male animals were exposed only during 6 weeks of premating phase, there were no exposure during mating and treatment of females was limited to gestation days 1-19 (F1 weaning period not included). The other information (iv) included only male animal exposure and during 1 day or 1 week. The study does not have a required exposure duration according to OECD TG 443 because the exposure does not cover mating/lactation/full exposure of the F1 generation starting *in utero* and continuing up to the adulthood. Therefore it does not fulfil the criteria set in OECD TG 443.

In the supporting information (ii, iii) you have provided, the animals were exposed to the test substance on gestation days 1-19. The other information (iv) you have provided was conducted in adult males. The study does not cover all relevant life stages as the animals were not exposed during lactation and postnatally. Therefore it does not fulfil the criteria set in OECD TG 443.

As explained in the Appendix "Reasons common to several requests" your adaptation according to Annex XI, Section 1.5 is currently rejected.

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

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

Premating exposure duration and dose-level setting

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

The draft decision requested mating the F1 animals of Cohort 1B to produce the F2 generation and thus a premating exposure duration for P0 animals of 2 weeks was deemed sufficient. The request for the production of the F2 generation was removed following your comments on the draft decision.

Ten weeks premating exposure duration is then required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration. [10]

Therefore, the requested premating exposure duration is at least 10 weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection

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

should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

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

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

Cohorts 1A and 1B

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

Species and route selection

ECHA agrees with your comments on the draft decision that the study must be performed in rats with oral[11] administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[12].

[11] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[12] ECHA Guidance R.7a, Section R.7.6.

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[13].

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[14].

[13] https://echa.europa.eu/practical-guides
[14] 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 08 April 2020.

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

ECHA took into account your comments and amended the requests. Additionally, ECHA removed the request for the EOGRT study, from Appendix A, 'Information required from all the Registrants subject to Annex IX of REACH'.

> Moreover, in your comments on the draft decision, you urge ECHA to postpone the decision regarding the request to undertake an OECD TG 443 study with propan-1-ol until results of the study with propyl acetate are available.
>
> ECHA notes that the read-across is only tentative at this stage. Furthermore, the deadline proposed for the present decision would allow sequential testing if needed.

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[15] 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)[16]

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

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

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

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

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

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

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

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

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

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

OECD Guidance documents[17]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

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

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

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

Appendix 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]
[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.