~~Confidential~~

Helsinki, 07 June 2023

Addressees
Registrant(s) of 1,4-Butanediol as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
02/02/2022

Registered substance subject to this decision ("the Substance")
Substance name: Butane-1,4-diol
EC/List number: 203-786-5

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 ***16 March 2026***.

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

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

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

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

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes IX and 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 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 on Reasons common to several requests

1. **Assessment of your read-across approach under Annex XI, Section 1.5.**

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your 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 document in CSR and an updated read-across justification attached to your comments to the draft decision.

You read-across between the structurally similar substances, gamma-butyrolactone, EC 202-509-5 (CAS 96-48-0) as source substance and the Substance (BDO) as target substance.

You have provided the following reasoning for the prediction of toxicological properties: *"Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) as precursors and surrogates for gamma-Hydroxybutyrate (GHB). Both GBL and 1,4-BD are metabolically converted to GHB. As such, the clinical presentation and management of GBL and 1,4-BD intoxication shares a great deal of common ground with that for GHB."*

Your updated read-across justification document provided with your comments reiterates the above reasoning and states that *"after uptake, BDO is rapidly metabolised by alcohol/aldehyde dehydrogenases to form γ-hydroxybutyric acid (GHB) which is the main metabolite also of the source substance γ-butyrolactone (GBL)"*, and that *"no additional adverse effects and/or organ-specific toxicity as those already identified in the available studies would be observed in a subchronic repeated dose toxicity study and a prenatal developmental toxicity study in a non-rodent species with the target substance."*

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

[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

properties of your Substance are predicted to be quantitatively equal to those of the source substance.

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

1. *Read-across hypothesis contradicted by existing data*

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[4] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". 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. The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

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

We have identified the following contradictions to your hypothesis:

a. *Differences in metabolism*

You have provided references to scientified publications to support your claim that the Substance is rapidly transformed via a non-common-compound to the source substance, with your comments. However, the references are made without further supporting information (i.e. full publications) and therefore no independent assessment can be perfomed by ECHA.

The publicly available summary of the reference Vree et al. 1978 (DOI: 10.1007/978-3-642-66925-5_9) indicates that the Substance in humans "*may show the expected advantages of a longer halflife time in clinical practice."* Vree et al. also describe that the metabolisation is limited by the capacity of the metabolising enzymes, and that the common compound "is consecutively metabolized by the same enzyme but apparently at a considerably lower rate."

This indicates that there is exposure to a non-common compound (aldehyde; see shortcoming 2 "missing supporting information on non-common compounds"). In addition to this difference, another publication (Fung et al, 2008; doi: 10.1208/s12248-007-9006-3) demonstrates that the half-life in rats after intravenous application leads to systemically available parent compound (the Substance) in the range of hours; at doses that are relevant to the information requirement (140 mkd; 571 mkd). This experimental data also indicates exposure to the non-common compound.

You have not established that an exposure in the range of hours can be considered rapid (bio)transformation to common compounds, and would not contradict your hypothesis.

b. *Differences in toxicity profiles*

Histopathology findings of urinary bladder differ between the target and source substances. Unique findings are indicated in the OECD TG 422 study with the target substance that were

[4] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

not indicated in the sub-chronic toxicity studies with the source substance in rat and mouse. More specifically, a diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder were observed in the 400 and 800 mg/kg groups of the OECD TG 422 study.

In your comments to the draft decision you state the following:

1. "*Histopathology findings in the bladder occurred at doses adversely affecting food consumption and body weight parameter, were of minimal severity and did not follow a dose-response relationship with regard to their severity*"
2. "*While histopathological changes in the urinary bladder were identified in the OECD TG 422 study in Sprague Dawley rats with BDO these were not observed in a 28d study with the same substance."*
3. *"Instead, microscopic changes were found in the liver (mild to moderate inflammation), which were not seen in the OECD TG 422 study."*
4. *"As the effects were inconsistent between the studies and toxicity is dominated by the effects on the central nervous system for both substances, the histopathological differences are considered to have no impact on the justification of the read-across approach."*

You have not provided the data to support your statements and ECHA is therefore unable to evaluate the severity and frequency of the histopathological findings. You also did not provide an explanation how the food consumption and body weight parameter relate to the histopathology findings in the bladder in the current case. Comment 1. is not having impact on the initial assessment by ECHA as it is submitted without supporting information and further explanation(s).

ECHA notes that the selected tissues for histopathologic evaluation in the 28-day repeated dose toxicity study with the Substance did not include bladder. Therefore your comment 2. does not have any basis as there is no possibility for comparison of bladder histopathology investigations between the two studies.

Sensitivities of different study designs using different rat strains might lead to differences or similarities in some types of toxicity. Comments 3. and 4. do not discredit the relevance of the bladder histopathology findings of the OECD TG 422 study because the 28-day study and the OECD TG 422 studies with the Substance were conducted with different rat strains. Different rat strains used in the studies potentially explain also studies exerting differing toxicity profiles in target organ liver because the metabolic capacity of liver and the following (bio)transformation products profile may be different between the Spraque Dawley strain used in the 28-day study and the Wistar strain used in the OECD TG 422 study. Comparison of the similarities and differences with the source 90-day studies is not conclusive as the studies were conducted again using different species and rat strain (B6C3F1 mouse and Fischer 344 rat), respectively.

In your comments to the draft decision you also state that the relation of the bladder histopathological findings to treatment "*remains unclear",* and that *"no historical control data of these findings were presented in the studies*." You also consider that the findings "*are considered to be of minor relevance in comparison to the effects on the central nervous system*."

You speculated, without substantiation, that the presence of a leading effect of toxicity for the substances, e.g. to the central nervous system/sedation, abrogates other differences in toxicity profiles, which must be rejected. Further, the purposes of the requested information requirements are to investigate pre-natal developmental toxicity, and to obtain repeated dose toxicity information that is expected to impact the study design of a future extended one-

generation toxicity study.

You have not demonstrated that the observed differences in toxicity profiles have no impact on the prediction of properties of the Substance.

c. *Conclusion on information that contradicts the hypothesis*

The available set of data on the target and source substances indicates differences in the (a) toxicokinetic and (b) toxicodynamic properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

2. *Missing supporting information on the formation of common and non-common compounds*

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 supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

Supporting information must include toxicokinetic information on the formation of the common compound and non-common compounds. Furthermore supporting information must be provided to characterise the contribution of the non-common compound on the prediction of properties of the Substance.

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound. In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds. Furthermore, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

In your comments to the draft decision you have provided references to scientified publications to support your claim that the Substance is rapidly transformed via a non-common-compound to the source substance. However, these literature references are made without further supporting information (i.e. full publications) and therefore no independent assessment can be perfomed by ECHA.

With regard to the formation of common compounds, you have not provided reliable experimental information about the (bio)transformation of the Substance nor the source substance(s) to support your claims regarding formation of a common compound.

With regard to the contribution of non-common compounds to the prediction of properties of the Substance, you have not provided reliable information characterising the exposure to the non-common compounds resulting from exposure to the Substance and to the source substance. The publicly accessible abstract of the reference (Vree et al. 1978) states that the conversion to the non-common compound (aldehyde) is faster than the conversion to the source substance. This is an indication that exposure to the non-common compound will occur. You have not included reliable information and an explanation addressing the impact

of exposure to these non-common compounds is included in the documentation of your read-across approach.

In the absence of this information, you have not provided supporting evidence establishing that the proposed common (bio)transformation product is formed as assumed in your read-across hypothesis. Also you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis which takes into account the effects of systemically available parent substance (the Substance) as well as non-common compounds. Therefore, you have not provided sufficient supporting information to scientifically justify your read-across hypothesis.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

2. Assessment of your Weight of Evidence adaptation under Annex XI, Section 1.2

You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

- Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

In your comments to the draft decision you state that "*the WoE approach is no longer defended by the lead registrant. Instead, key and supporting studies were identified and were used in a read-across approach.*"

ECHA has evaluated the related PDF attachment in your comments.

ECHA understands that the weight of evidence approach initially evaluated remains relevant for other addressees of the decision while the lead Registrant has changed their approach. Therefore the following evaluations have been carried out applying the initial approach and considering weight of evidence adaptations. The information provided through the key- and supporting studies as provided by the lead registrant in their comments is addressed by the evaluation of relevance- and reliability deficiencies.

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

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

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these

sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Appendices below.

These issues identified below are essential for all the information requirements in which you invoked a weight of evidence.

1. Reliability of the read across approach

Section 1 of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These finding apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

Additional issues related to weight of evidence are addressed under the corresponding endpoints.

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

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

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

You have provided an adaptation according to Annex XI, Section 1.2. Weight of Evidence in your dossier.

You have provided the following sources of information:

i) combined repeated dose toxicity study with reproductive/developmental toxicity screening test (1999) on the Substance
ii) sub-acute toxicity study (1990) on the Substance
iii) sub-chronic toxicity study (1992) in mice with source substance gamma-butyrolactone (EC 202-509-5)
iv) sub-chronic toxicity study (1992) in rat with source substance gamma-butyrolactone (EC 202-509-5)

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

A. Weight of evidence

As explained in Section 2 of the Appendix common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

The provided studies investigate the above mentioned key elements. Therefore, they provide information that would contribute to the conclusion on them.

However, the reliability of these studies is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information i) and ii) for this endpoint are also affected by the following issues:

The requirements of OECD TG 408 include:
1. At least 10 female and 10 male animals should be used at each dose level (including control group)
2. dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

The Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) i) you have submitted does not have the required exposure duration of 90 days as required in OECD TG 408, because the exposure duration of the screening test is approximately 63 days (for females) and 28 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using 5 animals per sex per group and not 10 per sex per group as in OECD TG 408.

The repeated dose oral toxicity study (OECD TG 407) ii) you provided does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 days, and it was conducted with less than 10 animals per sex per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408.

Taken together, the sources of information as indicated above, provide relevant but lacking/deficient information on the required exposure duration and number of animals investigated. Therefore, significant amount of essential information is lacking that would inform on sub-chronic toxicity (90-day) 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 sub-chronic toxicity (90-day). Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because although the information indicate that human exposure to the Substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure.

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

2. 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 a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

> *"According to Regulation (EC) 1907/2006, Annex IX Column 2, it is laid down that chronic tests on fish shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 1,4-Butuanediol reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore, and for reasons of animal welfare, a chronic test in fish is not provided*".

We have assessed this information and identified the following issues:

a) Your interpretation of the legal basis used in your justification is incorrect

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 fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

b) Animal welfare is not a legal basis to omit the required information

Animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

Therefore, your adaptation is rejected.

In the comments to the draft decision, you acknowledge that an adaptation based on Annex IX, Section 9.1., Column 2 is not adequate. You further indicate your intention to adapt the information requirement by using a weight-of-evidence approach according to Annex XI, section 1.2 of the REACH Regulation.

Together with your comments, you have provided the following sources of information that you intend to use for your weight-of-evidence approach:

a. a study according to OECD TG 204 with the Substance;
b. three QSAR predictions (Annex XI, Section 1.3.) for the Substance:
   (i) a prediction derived from model ECOSAR for chemical class "Neutral Organic" and for chronic toxicity to fish,
   (ii) a trend analysis based on a dataset of 9 long-term fish toxicity results (effect on growth) for 9 substances identified as "neutral organics",
   (iii) a trend analysis based on a dataset of 16 long-term fish toxicity results (effects on mortality) for 9 substances identified as "neutral organics".

As explained in Section 2 of the 'Appendix common to several requests', the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the property investigated by the required study.

To fulfil the information requirement of Annex IX, Section 9.1.6, a study performed according to OECD TG 210 must be provided. OECD TG 210 requires the study to investigate the following key parameters:

1. Stage of embryonic development,
2. Hatching and survival of embryos and larvae,
3. Survival of juvenile fish,
4. Abnormal appearance,
5. Abnormal behaviour (e.g. hyperventilation, uncoordinated swimming, atypical quiescence and atypical feeding behaviour),
6. Weight at the end of the test,
7. Length at the end of the test.

Concerning key parameters (1) '*Stage of embryonic development'*; (2) '*Hatching and survival of embryos and larvae'*; (4) '*Abnormal appearance'*; and (5) '*Abnormal behaviour'*, none of the sources of information provided investigate these key parameters. Therefore, they do not provide information that would contribute to the conclusion on these key parameters.

Concerning key parameter (3) '*Survival of juvenile fish'*, sources of information (a) and (b) may provide relevant information on survival of juvenile fish. However, the reliability of these sources of information is significantly affected by the following deficiencies:

- The conditions of exposure in OECD TG 210 specifies that the test should start as soon as possible after the eggs have been fertilised until species-specific time period that is necessary for the control fish to reach a juvenile life-stage (28-60-d post-hatch).

However, the test submitted as source of information (a) has a duration of 14 days. Therefore, the study duration is shorter than indicated in the OECD TG 210.

This condition of exposure is essential because the effects observed in a long-term study might be considerably more pronounced than over a shorter study duration. Therefore, the provided study cannot be considered a reliable source of information that could contribute to the conclusion on this key parameter investigated by the required study.

- As for sources of information (b), ECHA Guidance R.6.1.5.3. explains that a prediction is within the applicability domain of a model, if, among others, the substance for which the prediction is conducted falls within descriptor, structural, mechanistic, and metabolic domains.

  The 3 models used for sources of information (b)(i), (ii) and (iii) were developed based on training sets consisting of substances identified as "neutral organics", with a narcotic mode of action (baseline toxicity). Therefore, the mechanistic domain of these 3 models is limited to substances with a non-specific narcotic mode of action.

  However, you have not demonstrated that the mode of action of the Substance for long-term toxicity to fish is based only on a non-specific narcotic effect. In particular, the Substance was shown to affect the central nervous system in mammals. You explain in your dossier that the Substance is expected to be rapidly metabolised to gamma-hydroxybutyrate (GHB), which is chemically related to the brain neuro-transmitter GABA. This conversion is done by enzymes alcohol dehydrogenase and aldehyde dehydrogenase. Both enzymes, and the brain neuro-transmitter GABA are also present in fish. Therefore, it cannot be ruled out that the Substance could affect the central nervous system of fish with a specific mode of action involving neuro-transmitter GABA. Furthermore, the substances used in the training sets of the 3 models have very low calculated structural similarities with the Substance and there are no indications that the substances in the training sets could lead to the same relevant metabolites as those for the Substance. Therefore, you have not demonstrated that the Substance is inside the applicability domains for any of the 3 models.

Concerning key parameters (6) '*Weight at the end of the test'* and (7) '*Length at the end of the test'*, sources of information (b)(i) and (b)(ii) may provide relevant information on the effects of neutral organic substances on weight and length of fish at the end of the test. However, as explained above, the reliability of these sources of information is significantly affected.

Taken together, the sources of information attached to your comments provide information on long-term toxicity to fish, but essential parts of the information requirement is lacking (stage of embryonic development, hatching and survival of embryos and larvae, abnormal appearance and behaviour). Furthermore, the information provided on survival, weight or length of juvenile fish is not reliable. Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether the Substance has or has not the properties foreseen to be investigated in an OECD TG 210 study.

Therefore, 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 adaptation under Annex XI, Section 1.2. Weight of Evidence in your dossier.

You have provided the following sources of information:

i) pre-natal developmental toxicity study (1994) in mouse with the Substance via oral route
ii) combined repeated dose toxicity study (1999) with reproductive/developmental toxicity screening test in rats on the Substance via oral route
iii) pre-natal developmental toxicity study (1988) in rat with source substance gamma-butyrolactone (EC 202-509-5) via oral route
iv) pre-natal developmental toxicity study (1993) in rabbit with source substance gamma-butyrolactone (EC 202-509-5) via inhalation route.

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

A. Weight of evidence

As explained in Section 2 of the Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfill the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) prenatal developmental toxicity in two species, including foetal survival (number of live foetuses, number of resorptions and dead foetuses, postimplantation loss), and structural malformations and variations (external, visceral and skeletal), 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

The provided sources of information ii) to iv) investigate the above mentioned key parameters in a second species. Therefore, they provide information that would contribute to the conclusion on this key parameter in a second species.

First, the source ii) provides limited information on developmental toxicity covering some aspects such as survival, body weights and clinical signs, and covers maternal toxicity and maintenance of pregnancy in a second species. The source ii) does however not investigate the prenatal developmental toxicity key parameters on foetal survival, and structural malformations and variations as required in a pre-natal developmental toxicity study (OECD TG 414). Therefore, no conclusion can be drawn on prenatal developmental toxicity as required by the information requirement.

Second, the conditions of OECD TG 414 include the following:

a) the exposure duration is at least from implantation until one day prior to scheduled caesarean section.

In study iv):

a) the exposure was only until gestation day 19 whereas the caesarean section was performed on gestation day 29.

The reliability of source iv) is therefore limited by the short exposure duration and no conclusion can be drawn on prenatal developmental toxicity as required by the information requirement based on this study.

Further, the reliability of the sources of information iii) and iv) is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

Taken together, even if these sources of information provide information on the key parameters, their reliability 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 dangerous property foreseen to be investigated by the required study.

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

Information on study design

A PNDT study according to the OECD TG 414 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 (mouse). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study shall be performed with oral[5] administration of the Substance.

[5] 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[6].
4. Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

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[7].

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

Appendix D: Procedure

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (EOGRTS; Annex X, 8.7.3.), however this testing proposal is on hold pending the receipt of the data requested under section A.1. of this decision. This is because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the EOGRTS. Therefore, you are required to perform the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your EOGRTS testing proposal. You should include a justification for the study design according to ECHA Guidance R.7a, Section R.7.6., taking into account the results of the Sub-chronic toxicity study (90-day).

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 04 March 2021.

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

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

In your comments, you requested an extension of deadline. The deadline of the draft decision was set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended to 30 months to take into account currently longer lead times in contract research organisations.

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[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[10]

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[11]

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