~~Confidential~~

Helsinki, 03 May 2022

Addressees
Registrants of JS_Isovaleraldehyde_590-86-3 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
03/09/2010

Registered substance subject to this decision ("the Substance")
Substance name: Isovaleraldehyde
EC number: 209-691-5

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 the deadline of ***8 February 2024***.

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

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

1. In vitro study(ies) for serious eye damage/eye irritation (Annex VII, Section 8.2., following the testing strategy as outlined in OECD GD on an Integrated Approach on Testing and Assessment for Serious Eye Damage and Eye irritation. Series on Testing and Assessment No.263TG 405)

2. Skin sensitisation (Annex VII, Section 8.3.)

   i. in vitro/in chemico skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.); and

   ii. Only if the in vitro/in chemico test methods specified under point 2.i.) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, in vivo skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);

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

4. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

5. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

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

- Appendix entitled "Reasons common to several requests";

- Appendix entitled "Reasons to request information required under Annexes VII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH, the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;

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 analogue 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:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Skin sensitisation (Annex VII, Section 8.3)

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.

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 not provided a read-across justification document. You have provided the OECD SIDS document (2000) which contains a hypothesis but no further justification.

You read-across between the structurally similar substances,

- valeraldehyde, EC No. (CAS No.),
- butyraldehyde, EC No. 204-646-6 (CAS No. 123-72-8),
- isobutyraldehyde, EC No. 201-149-6 (CAS No. 78-84-2),
- propionaldehyde, EC No. 204-623-0 (CAS No. 123-38-6),
- 2-methyl butyraldehyde, EC No. 202-485-6 (CAS No. 96-17-3), and
- 3,5,5-trimethylhexanal, EC No. 226-603-0 (CAS No. 5435-64-3)

as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: " *[…] the relatively uniform toxicity profiles of aldehydes allow an estimation of these endpoints on the basis of data and results, which have been obtained during the investigation of other structurally related aldehydes, such as propionaldehyde, n-butyraldehyde and isobutyraldehyde.*"

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source

[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

substance.

ECHA has assessed this information and identified the following issues:

1. *Absence of read-across documentation*

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

Your read-across hypothesis is based on citing similarity in toxicological profiles of the source substance(s) and the Substance. In addition you have not provided any justification to support your hypothesis. You consider that these elements are a sufficient basis for predicting the (eco)toxicological properties of the Substance.

You have not substantiated how similarity in these properties alone would explain similarity in the predicted endpoint(s) and thus be sufficient to justify the toxicological predictions. In addition, you have not provided documentation that would compare any of the properties of the source substances with those of the Substance.

Similarity in structure or physico-chemical properties alone does not necessarily lead to predictable or similar human health properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological or ecotoxicological property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances.

2. *Adequacy and reliability of source studies*

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

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

Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections A.2 and A.3. Therefore, no reliable predictions can be made for these information requirements.

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:

- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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 following deficiency is common to all information requirements for which you invoked a weight of evidence adaptation. Deficiencies specific to certain information requirements are addressed under the respective sections in the Appendices below.

- <u>Reliability of the read across approach</u>

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. These deficiencies affect significantly the reliability of the sources of information relating to analogue substances.

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

1. In vitro study for serious eye damage/irritation

In vitro serious eye damage/eye irritation is an information requirement under Annex VII (Section 8.2.).

You have provided the following information on the Substance:
i. Key study, in vivo eye irritation study based on internal method ([redacted], 1974)
ii. Supporting study, in vivo eye irritation study, non-guideline ([redacted], 1974)

We have assessed this information and identified the following issues:

A. Assessment of whether the Substance causes damage to the eyes

To fulfil the information requirement under Section 8.2., Column 1 to the REACH Regulation, both serious eye damage and eye irritation needs to be covered.

You have provided two non-guideline compliant studies (studies i and ii), based on which you conclude that the substance causes eye irritation and you have self-classified the substance as Eye Irrit. 2.

ECHA agrees that the substance causes damage to the eyes.

B. Assessment of whether the damage caused by the Substance is reversible or irreversible

Study not conducted using a recognised test method

Toxicological and eco-toxicological tests on substances must be conducted in compliance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or ECHA as being appropriate (Article 13(3) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided study (i) has been performed using an internal method that does not comply with internationally acknowledged tests guidelines. In that study, dose volume of 50 µl was used, that is lower than the dose volumes used in test guidelines (100 µl) and hence can lead to underestimation of the hazardous property.

In addition, you have provided a study (ii) which you assigned with reliability 3. We agree that this study is unreliable.

The data show that Substance is causing damage to the eyes, however due to the issues raised above, irreversible reactions cannot be excluded.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision, you agree to provide the information.

Information on the study design

To fulfil the information requirement for the Substance, the *in vitro* test methods listed in the testing strategy (outlined in the OECD GD titled 'an Integrated Approach on Testing and

Assessment for Serious Eye Damage and Eye irritation Series on Testing and Assessment No.263') must be followed. As specified in Annex VII, Section 8.2.1, column 2, if results from a first *in vitro* study does not allow a conclusive decision on the classification of a substance or on the absence of eye irritation potential, (an)other in vitro study/ies) for this endpoint shall be considered.

2. Skin sensitisation

Skin sensitisation is an information requirement under Annex VII to REACH (Section 8.3.). Under Section 8.3., Column 1, the registrants must submit information allowing (1) A) a conclusion whether the substance is a skin sensitiser and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and (2) risk assessment, where required.

To fulfil the information requirement, as specified in the Annex VII, Section 8.3., Column 1 to the REACH Regulation, the following aspects must be covered: A) whether the Substance causes skin sensitisation, and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the Substance is considered to be a skin sensitiser.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence), based on which you conclude that the Substance is a Category 1 skin sensitiser.

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

i. modified Local Lymph Node assay with the analogue substance propionaldehyde (EC 204-623-0) ([redacted] 2004)
ii. OECD TG 406 with the analogue substance propionaldehyde (EC 204-623-0) ([redacted], 1999).
iii. OECD TG 406 with the analogue substance propionaldehyde (EC 204-623-0) ([redacted], 1999).
iv. OECD TG 406 with the analogue substance butyraldehyde (EC 204-646-6) ([redacted], 1981).
v. Mouse Ear Swelling Test with the analogue substance 2-methylpropanal (EC 201-149-6) ([redacted], 1990).
vi. OECD TG 429 with the analogue substance 2-methylbutanal (EC 202-485-6) ([redacted], 2008).
vii. OECD TG 406 with the analogue substance 3,5,5-trimethylhexanal (EC 226-603-0) ([redacted], 1997).
viii. *in silico* prediction (viii) based on a publication (2008)

As explained in the Appendix on Reasons common to several requests your weight of evidence adaptation under Annex XI, Section 1.2. is rejected. Nevertheless, ECHA has assessed the provided sources of information and has identified the following issues.

A) Assessment whether the Substance causes skin sensitisation

Information that can be used to support weight of evidence adaptation for information requirement of Section 8.3 at Annex VII includes similar information that is investigated by *in vitro*, *in chemico* and/or *in vivo* test methods. These key investigations include:

- investigation of cell proliferation in the draining lymph nodes (local lymph node

assay), investigation of local responses in animals or humans (guinea pig assays or human studies), or investigation of molecular interaction with proteins, inflammatory response in keratinocytes and activation of dendritic cells (in vitro and in chemico assays).

The sources of information (i to viii) provide relevant information, as they aim to provide information on the key investigations. However, these sources of information have the following deficiencies affecting their reliability.

While the source of information (i to viii) provide relevant information on skin sensitisation, these sources of information have the following deficiencies affecting their reliability.

i. Read-across rejection

As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5. is rejected for the studies (i) to (viii).

ii. Incompliant robust study summary (study viii)

Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Information on the reporting needs are specified in the respective OECD test guidelines under section "Test report".

In your registration dossier you have provided information (viii) derived from experimental data from a group of substances generated using a SAR-based approach.

You have not provided robust study summaries for any of the studies listed under study viii. This deficiency significantly affects the reliability of this source of information and therefore its ability to predict the properties of the Substance.

iii. Studies i. and v. not conducted using a recognised test method

Toxicological and eco-toxicological tests on substances must be conducted in compliance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or ECHA as being appropriate (Article 13(3) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided study (ii) was not based on OECD TG 429 and appears to be based on Modified LLNA (IMDS = Integrated Model for the Differentiation of Skin Reactions), albeit not specified by you. This IMDS test method has not been validated or considered to be scientifically valid by international bodies in respect to how and what measurements are performed and what is the appropriate cut off value for positive predictions.

The provided study (v) Mouse Ear Swelling Test (MEST) appears to have gone through some validation in the 1980's, however the test has never been included in an EU method regulation or OECD test guidelines due to specific limitations. The OECD TG 406 states in addition in paragraph 4 that in case a negative results is obtained in the MEST, additional information on sensitisation potential needs to be generated.

These studies (i and v) were not conducted using a recognised method. This deficiency significantly affects the reliability of these sources of information and therefore its ability to predict the properties of the Substance.

In summary, despite their relevance, studies i. to viii. have significant reliability issues and even when combined they are low total weight and do not allow any conclusion on the information requirement (dangerous property) to be drawn.

Conclusion

As explained above, 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 skin sensitisation studies.

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

B) Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

No assessment of potency

To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section A above), this condition cannot be assessed.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you reiterate the studies already provided in your registration dossier (specifically studies vi and viii), and reiterate your adaptation of the information requirement according to Annex XI, Section 1.5. You present a strategy relying on the generation of additional supporting information on the Substance and on the analogue substances. You indicate your intention to provide this in a future update of your registration dossier.

ECHA acknowledges your intentions to refine your read-across approach and submit a "*well justified read-across approach*". This strategy relies essentially on data which is yet to be provided, therefore no conclusion on the compliance can currently be made. Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation). Currently, the data gap remains and you remain responsible for complying with this decision by the set deadline.

Concerning your comment related to possible testing strategy, in case the read-across approach which you intend to provide is not accepted by ECHA, ECHA notes that the validation of GARDskin and GARDpotency has been finalised. GARDskin was considered appropriate to support the discrimination between skin sensitisers (Cat 1) and non-sensitisers, however not as a stand-alone assay. The GARDpotency assay is not yet considered as a scientifically valid

method and its use in its current form is not supported[4]. Therefore, GARDskin assay could be used as a supporting element together with other in vitro/in chemico studies in a testing strategy, but the use of GARDskin is not recommended on its own. Kinetic DPRA, as included in the OECD TG 442C, can provide supporting evidence of skin sensitisation potency either as a stand-alone assay or together with other information, as indicated in the respective test guideline.

Information on the study design

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, OECD TG 442D and EU Method B.71/OECD TG 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (EU Method B.42/OEDC TG 429) is considered as the appropriate study.

3. In vitro gene mutation study in bacteria

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

You have adapted thisinformation requirements by applying weight-of-evidence approaches in accordance with Annex XI, Section 1.2. In support of your adaptation you have provided the following sources of information:

i. a non-GLP *in vitro* gene mutation study in bacteria according to OECD TG 471 with the Substance ([redacted], 1980);
ii. a non-GLP *in vitro* gene mutation study in bacteria similar to OECD TG 471 with the Substance ([redacted], 1989);
iii. an *in vitro* gene mutation study in bacteria according to OECD TG 471 (GLP not specified) with the analogue substance valeraldehyde (EC No. 203-784-4; CAS RN 110-62-3) ([redacted], 1988);
iv. a non-GLP *in vitro* gene mutation study in bacteria similar to OECD TG 471 with the analogue substance butyraldehyde (EC No. 204-646-6; CAS RN 123-72-8) ([redacted], 1986);
v. an *in vitro* gene mutation study in bacteria similar to OECD TG 471 (GLP not specified) with the analogue substance isobutyraldehyde (EC No. 201-149-6; CAS RN 78-84-2) ([redacted], 1999);
vi. a non-GLP *in vitro* gene mutation study in bacteria according to OECD TG 471 with the analogue substance propionaldehyde (EC No. 204-623-0; CAS RN 123-38-6) ([redacted], 1986)

As explained in the Appendix on Reasons common to several requests, it would be sufficient to reject your weight of evidence adaptation based on the fact that you have not submitted any justification of your adaptation.

In any case, to fulfil the information requirement, normally a study performed according to OECD TG 471 must be provided. OECD TG 471 investigates gene mutations in bacteria as a key parameter using 5 different bacterial strains.

The sources of information (i.) to (vi.) provide relevant information on *in vitro* gene mutations in bacteria. The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98;

[4] ESAC opinion on the scientific validity of the GARDskin and GARDpotency test methods, No. 2021-01 of 8 July 2021

TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). The reported data for the individual studies you have provided included results for TA98 (studies i, ii, iii, iv, v and vi)/TA100(studies i, ii, iii, iv, v and vi)/TA1535(studies i, iii, iv and v)/TA1537 or TA97a or TA97(studies i, iii, iv, v and vi)/the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) (studies ii and v).

However, the reliability of these sources of information is significantly affected by the following deficiencies:

1) *Your read-across adaptation is rejected*

   Information from source substances can contribute to weight of evidence adaptation only if the read-across is acceptable. Studies (iii.) to (vi.) are performed with analogue substances. However, for the reasons explained under section 2 of the Appendix on Reasons common to several requests, the provided studies performed on source substances cannot be considered reliable sources of information that could contribute to the conclusion on the key parameters investigated by the required OECD TG 471.

2) *The studies provided have critical deficiencies*

   The specifications of OECD TG 471, include the following:

   a. The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.

      However, the reported data for the studies (i and iv) you have provided did not include a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance.

   b. At least 5 doses must be evaluated, in each test condition

      However, the reported data for the study (v) you have provided did not include the evaluation of at least 5 doses in each test condition.

   c. Triplicate plating must be used at each dose level.

      However, the reported data for the studies (ii and iii) you have provided did not include triplicate plating at each dose level.

   d. One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.

      However, the reported data for the studies (i, ii, iii, iv, v, vi) you have provided did not include a positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.

   e. The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.

However, the reported data for the studies (i, ii, iii, iv, v, vi) you have provided did not include a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory.

f. The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

However, the reported data for the studies (i, ii, iv, vi) you have provided did not include data on the number of revertant colonies per plate for the treated doses and the controls.

Taken together, even if these sources of information provide information on gene mutations in bacteria, 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 in an OECD TG 471. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

In your comments to the draft decision, you have agree to provide the information.

Information on the study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed.

4. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

You have provided the following information:

i. a short-term toxicity test on aquatic invertebrates according to EU Method C.2 with the Substance ([redacted], 1989)

We have assessed this information and identified the following issue:

To fulfil the information requirement, a study must comply with OECD TG 202 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Characterisation of exposure

- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 80 to 120 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);

Reporting of the methodology and results

- the methods used to prepare stock and test solutions is reported;

Your registration dossier provides a study showing the following:

Characterisation of exposure
- no analytical monitoring of exposure was conducted;

Reporting of the methodology and results
- the methods used to prepare stock and test solutions is not reported;

Based on the above,
- the Substance is difficult to test due to its high volatility and there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically, no analytical monitoring was performed and no indications on preventive action to avoid loss of the Substance during the test. Therefore you have not demonstrated that effect values can be reliably expressed based on nominal concentrations.
- The reporting of the study is not adequate. More, specifically, you have not described how test solution were prepared. Therefore, you have not demonstrated that the test solution preparation was adequate to minimise losses from the test medium taking into account the properties of the Substance (high volatility).

Therefore, the requirements of OECD TG 202 are not met.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision, you have agree to provide the information.

Study design

The Substance is difficult to test due to the volatility of the Substance (vapour pressure of 75 hPa at 20°C). OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

5. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

You have provided the following information:
i. a growth inhibition study on algae according to DIN 38412 (part 9) with the Substance ([redacted], 1989)

We have assessed this information and identified the following issue:

To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Characterisation of exposure

- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.
- For volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24 hour intervals is required.
- the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within 80 to 120 % of the nominal or measured initial concentration throughout the test;

Reporting of the methodology and results

- the test conditions are reported (*e.g.*, composition of the test medium);
- the methods used to prepare stock and test solutions is reported;
- the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

Other considerations

- Algal biomass is determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (*e.g.* flow cytometry, *in vitro* or *in vivo* fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test.

Your registration dossier provides a study showing the following:

Characterisation of exposure

- no analytical monitoring of exposure was conducted;

Reporting of the methodology and results

- the composition of the test medium is not reported;
- the methods used to prepare stock and test solutions is not reported;
- the results of algal biomass is only provided as average replicates values. No information on biomass in each flask at least daily during the test period is provided;

Other considerations

- you report that algal biomass was determined using epifluorescence,. However, you have not reported evidence of correlation between the measured parameter and dry weight;

Based on the above,

- the Substance is difficult to test due to its high volatility and there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically, no analytical monitoring was performed and no indications on preventive action to avoid loss of the Substance during the test. Therefore you have not demonstrated that effect values can be reliably expressed based on nominal concentrations.
- The reporting of the study is not adequate. More, specifically, you have not described the composition of the test medium. Also, you have not described how test solution were prepared. Therefore, you have not demonstrated that the test solution preparation was adequate to minimise losses from the test medium taking into account the properties of the Substance (high volatility). Finally, you have not provided adequate reporting of biomass data and validation data to demonstrate that the method used to monitor algal

biomass provide reliable information. On this basis, it cannot be verified whether the study meets the validity criteria of OECD TG 201 and provides a reliable basis to determine effects values.

Therefore, the requirements of OECD TG 201 are not met.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision, you have agree to provide the information.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.4.

Appendix B: 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[5].

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[6].

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

Appendix C: 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 04 May 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 requests.

In the comments to the draft decision, you requested an extension of the deadline to provide information from 12 to 18 months from the date of adoption of the decision. You considered that the extension of 6 months is needed due to the extra time needed due to the difficulties to conduct the test with a volatile substance.

ECHA acknowledges the difficulties in conducting the test for difficult to test methods.

On this basis, ECHA has granted the request and extended the deadline to 18 months.

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

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

Appendix D: List of references - ECHA Guidance[7] 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)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]

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

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.