EUROPEAN CHEMICALS AGENCY

Helsinki, 18 May 2020

Addressees
Registrants of JS_705-86-2_[redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
30 April 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Decan-5-olide
EC number: 211-889-1
CAS number: 705-86-2

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***23 August 2021***.

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. In vitro study for skin corrosion/irritation (Annex VII, Section 8.1.; test methods: OECD TG 430/431/435 and OECD TG 439) with the Substance;

2. In vitro study for serious eye damage/irritation (Annex VII, Section 8.2., following the testing strategy as outlined in the supplement to test method OECD TG 405) with the Substance;

3. Skin sensitisation (Annex VII, Section 8.3) with the Substance

   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 (OECD TG 442E) (Annex VII, Section 8.3.1.); and

   ii) Only if the *in vitro/in chemico* test methods specified under point 3.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) with the Substance.

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

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

6. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance;

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Only if the results in Annex VII, Section 8.1. (request A.1.) are not adequate for classification and risk assessment, *in vivo* skin corrosion/irritation (Annex VIII, Section 8.1., column 2.; test method: OECD TG 404) with the Substance;

2. Only if the results in Annex VII, Section 8.2. (request A.2.) are not adequate for classification and risk assessment, *in vivo* serious eye damage/eye irritation (Annex VIII, Section 8.2., column 2.; test method: OECD TG 405) with the Substance;

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

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method OECD TG 203) with the Substance.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Failure to comply

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

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on general considerations

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

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.); and
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.).

ECHA has considered the scientific and regulatory validity of your read-across approaches 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].

Assessment of predictions(s)

You have not provided a read-across justification document.

You read-across from
[1] ethyl butyrate, EC No. 203-306-4 (CAS No. 105-54-4);
[2] bis (2-ethylhexyl) adipate, EC No. 203-090-1 (CAS No. 103-23-1); and
[3] decanal, EC No. 203-957-4 (CAS No. 112-31-2)

as source substances to the Substance as target substance.

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

Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used, adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[4]

[2] ECHA Guidance, Read-Across Assessment Framework (RAAF).
[3] ECHA Guidance, Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs.
[4] ECHA Guidance R.6, Section R.6.2.6.1

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance.

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

Structural similarity
Annex XI, Section 1.5. specifies that whenever a read-across approach is used, 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.

You read-across from
[1] ethyl butyrate, EC No. 203-306-4 (CAS No. 105-54-4);
[2] bis (2-ethylhexyl) adipate, EC No. 203-090-1 (CAS No. 103-23-1); and
[3] decanal, EC No. 203-957-4 (CAS No. 112-31-2)

as source substances to the Substance (decan-5-olide; CAS No. 705-86-2) as target substance.

The target substance is a cyclic carboxylic ester, containing a 1-oxacycloalkan-2-one structure, while the source substances are aliphatic carbons with carboxylic acid ester or aldehyde functional groups. You have not addressed these structural differences and their impact on the likelihood that the substances have similar toxicological properties.

Conclusions on the grouping of substances and read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the proposed analogue substance(s). 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.

(ii) Assessment of Qualitative or Quantitative Structure Activity Relationship ((Q)SAR) adaptation, under the requirements of Annex XI, Section 1.3.

You have provided (Q)SAR adaptations in accordance with Annex XI, Section 1.3 for the following standard information requirements:

- In vitro skin corrosion/irritation (Annex VII, Section 8.1.); and
- Skin sensitisation (Annex VII, Section 8.3.).

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

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

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the

applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have not provided any documentation for the QSAR predictions. In particular, you have not included a QMRF and a QPRF in your technical dossier for the relevant endpoints. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

The adaptation you provided does not fulfil the criteria specified in Annex XI, Section 1.3. and it is therefore rejected.

Appendix A: Reasons for the requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. In vitro skin corrosion/irritation (Annex VII, Section 8.1.)

An *in vitro* Skin corrosion/irritation is a standard information requirement under Annex VII, Section 8.1. to the REACH Regulation.

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information with a view to whether it complies with the requirements for an adaptation under Annex XI, Section 1.2 of REACH (weight of evidence).

To cover the endpoint, you have provided the following *in vitro, in vivo* and QSAR study records with the Substance:

i. [redacted] 2017 – Key study. *In vivo* acute dermal toxicity (OECD TG 402; GLP) in rats.
ii. [redacted] 2018 - Key study. *In vitro* skin irritation reconstructed human epidermis test method using Epi Derm 200 (OECD TG 439; non-GLP compliant).
iii. US Army Environmental Hygiene Agency, 1978 - Supporting study. A non-guideline *in vivo* skin irritation study with the Substance. Neat substance applied for 24h to intact and abraded skin of six New Zealand White rabbits.
iv. D. L. J Opdyke, 1979 – Supporting study. A non-guideline *in vivo* skin irritation study in rabbits with the Substance. Neat substance applied for 24h to abraded rabbit skin.
v. D. L. J Opdyke, 1979 – Supporting study. A non-guideline *in vivo* skin irritation study with the Substance in humans. 1% in petrolatum with 48h exposure.
vi. Danish Environmental Protection Agency (Q)SAR database study for the Substance, 2018 – Supporting study. (Q)SAR predictions for skin irritation estimated by four different models i.e. Battery, Leadscope, SciQSAR and CASE Ultra within Danish QSAR database.

In your comments to the draft decision you provided information on *in vitro* and *in vivo* studies conducted with the analogue substance delta-dodecalactone, EC No. 211-932-4 (CAS No. 713-95-1):

vii. Acute dermal irritation/corrosion study according to the OECD TG 404;
viii. In vitro skin irritation study according to the OECD TG 439;
ix. "Read-across justification for CAS no. 705-86-2".

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the Substance is not irritating to the skin.

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently,

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

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

You have not provided a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

The sources of information must provide sufficient weight of evidence to conclude that the information requirement for skin corrosion/irritation, as specified in all of the available test guidelines (*in vitro* and *in vivo*[5]) are fulfilled by integrating and weighing the evidence e.g. the following aspects are covered:

1) whether the substance causes damage to the skin, and
2) in case of skin damage, whether the damage noted is reversible (irritation) or irreversible (corrosion).

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties and identified the following deficiencies:

Assessment if the Substance causes damage to the skin

You have provided information on eight (i-viii) studies addressing whether the substance causes damage to the skin. The studies i, iii, and v-vii resulted in negative prediction and the studies ii, iv and viii in positive predictions.

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

A. To fulfil the information requirement, the study has to meet the requirements of OECD TG 404. Among others the key parameters of this test guideline include:

   a) Suitable animal species (albino rabbit is the preferred laboratory animal, in case other species used, rationale needs to be provided);
   b) Number of animals: for corrosive materials one animal and for non-corrosive substances three animals;
   c) Concentration used: 0.5 ml for liquids or 0.5 g for solids at application site of approximately 6 cm^2 (ca. 80 mg/ cm^2 or 80 µL/ cm^2);
   d) Observation period: in the first animal until day 14, unless corrosion develops earlier, in the remaining two animals at least for 72h or up to 14 days, unless reversibility is seen before day 14; and
   e) Scoring of responses at 60 minutes, then 24, 48 and 72 hours after patch removal.

[5] OECD TGs 430, 431, 439 and 404

You have provided an *in vivo* acute dermal toxicity study (i) up to a 2000 mg/kg bw/day (ca. 20 mg/cm^2) in rats, and two *in vivo* skin irritation studies in rabbits (iii and iv) evaluating skin irritation at 24 hours after application of the Substance.

The reported data for the *in vivo* skin corrosion/irritation studies (i, iii and iv) did not include

a) Suitable animal species or rationale for choosing other species (study i)
b) Information on the number of animals (study iv)
c) Adequate concentration used (studies i) or sufficient information to evaluate the concentration used (study iii)
d) Adequate observation period (studies iii and iv)
e) Scoring of responses (studies iii and iv)

Therefore, the provided *in vivo* skin irritation studies do not cover the key parameters needed for an *in vivo* skin irritation study. Suitable animal species (the rat skin is not as sensitive as the rabbit skin and can underestimate the irritation potential), adequate exposure concentrations (low concentrations may underestimate irritation potential), and adequate observation periods (observation period too short for delayed reactions) are critical aspects for the sensitivity of the test system to detect potential damage to the skin induced by the test substance. In addition, information on the number of animals is critical for evaluation of statistical power of the study, while the tissue irritation scores are critical for evaluation of the severity of the effects. Due to these deficiencies, the provided information cannot be considered reliable sources of information that could contribute to the conclusion on whether the Substance causes damage to the skin.

B. To fulfil the information requirement, the study has to meet the general requirements for human studies. Among others, the key parameters of these studies include[6],[7]:

a) Information on the number and health status of the human volunteers;
b) Justification for the dose level selection; and
c) Details on exposure conditions (area of exposure).

You have provided a non-guideline *in vivo* skin irritation study (v) in humans conducted with 1% of the Substance in petrolatum with 48h exposure.

The reported data for the study (v) did not include any of the above mentioned information. Therefore, the provided study does not cover the key parameters needed for human studies assessing skin irritation and is not considered reliable.

C. Qualitative or Quantitative structure activity relationship ((Q)SAR)) adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.3. are fulfilled.

You have provided (Q)SAR predictions for skin irritation (vi). However, as explained under General considerations, your ((Q)SAR adaptations are rejected.

D. Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP, Directive 2004/10/EC) or other international standards recognised as being equivalent by the Commission or ECHA, and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

[6] ECHA Guidance R.7a, section R.7.2.4.2
[7] Guidance on the Application of CLP criteria, version 5.0, July 2017, section 3.2.2.1.1

Based on the information in your dossier, the provided *in vitro* skin irritation study (ii) was conducted after 1 August 2008 (report date 29 June 2018), but not performed according to GLP. Therefore, the provided study is not considered reliable.

E. Regarding the information on similar substances submitted with your comments, ECHA notes the following shortcomings with regards to the prediction of toxicological properties.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents[2, 3].

Read-across hypothesis
A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[8]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity and similarity in physico-chemical properties between the source substances and your Substance is a sufficient basis for predicting the properties of your Substance.

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

However, similarity in chemical structure and similarity of physicochemical properties does not necessarily lead to predictable or similar human health properties. You have not explained why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern. Therefore, a well-founded hypothesis to establish a reliable prediction for a potential to damage the skin, based on recognition of the structural differences between the source substance(s) and your Substance, is missing.

Adequacy and reliability of the information on the 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 should:

- 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); and
- 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.

[8] ECHA Guidance R.6.

In addition, Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including, among others, robust study summary(ies) of the source study(ies).[9]

A robust study summary must cover sufficient information to make an independent assessment of the study.[10]

In your comments to the draft decision, you have provided short descriptions of the source studies. However, you have not provided robust study summaries that allow independent assessment of the study.

In the absence of such documentation, ECHA cannot verify that the results to be read across meet the criteria above. The information on the analogue substances does therefore not provide reliable information for weight of evidence.

Based on the assessment (A-E) above, your weight of evidence adaptation does not include any reliable sources of information to conclude on the property damage to the skin.

Integrating and weighing the evidence for skin irritation potential

Taken together, the relevant sources of information, as provided in your registration dossier, show contradictory information on damage to the skin. While all studies provide some relevant information on the damage to the skin, studies resulting in both positive and negative findings have deficiencies that increase the uncertainty and are not considered reliable. Therefore, the weight of the contradictory information sources are considered low.

In your comments to the draft decision, also relying on new information submitted with them, you propose that the *in vitro* study (ii) indicating damage to the skin is likely to provide a false positive results due to the lack of damage to the skin demonstrated in the guideline *in vivo* studies (i, vii). ECHA acknowledges that the information proivided with the analogue substance indicate that the *in vitro* results (ii and viii) may be false positive. However, in the absence of reliable information (see point E above) allowing prediction of preperties from the analogue substance, this cannot be confirmed.

Accordingly, 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 for skin irritation potential, as specified in all of the available test guidelines (*in vitro* and *in vivo*[5]). Therefore, no conclusion on skin irritation potential can be made.

Assessment whether the damage caused by the Substance is reversible or irreversible

You have provided three studies (ii, iv and viii) indicating that the substance causes damage to the skin. However, none of the information sources, alone or together, provide any information on the reversibility or irreversibility of the damage to the skin. Therefore, no conclusion on whether the damage caused by the Substance is reversible or irreversible can be made.

[9] ECHA Guidance R.6, Section R.6.2.6.2
[10] How to report robust study summaries Practical Guide 3, Version 2.0 – November 2012

Conclusion on the weight of evidence
Your weight of evidence adaptation does not include any reliable source of information to conclude whether the Substance causes damage to the skin, or whether the observed damage is reversible or irreversible. Therefore, your adaptation is rejected and additional information on addressing skin corrosion and irritation is needed.

To fulfil the information requirement for the Substance, *in vitro* skin corrosion study (OECD TG 430/431/435) and *in vitro* skin irritation study (OECD TG 439) are considered suitable.

2. In vitro study for serious eye damage/irritation (Annex VII, Section 8.2.)

An *In vitro* serious eye damage/eye irritation is a standard information requirement in Annex VII, Section 8.2.1. of the REACH Regulation.

You have provided the following key studies in your registration dossier:

i. [redacted] 2018 - Key study. EpiOcular™ Eye Irritation Test (EIT) (OECD TG 492; non-GLP compliant).
ii. US Army Environmental Hygiene Agency, 1978 - Key study. A non-guideline *in vivo* eye irritation study (Klimish score 4 assigned).

We have evaluated the provided information and identified the following issues:

A. Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP, Directive 2004/10/EC) or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

   Based on the information in your dossier, the provided *in vitro* eye irritation study (i) was conducted after 1 August 2008, but not performed according to GLP. Therefore, the provided study is rejected.

B. Section 8.2.1., column 2 of Annex VII specifies that if results from a first *in vitro* study do 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.

   Additionally, the paragraph 46 of the OECD Guideline 492 states *"If the mean percent tissue viability after exposure and post-exposure incubation is less than or equal (≤) to the established percentage tissue viability cut-off value, no prediction can be made from this result in isolation, as shown in Table 4. This is because in case of a true positive, the methods cannot resolve between UN GHS Categories 1 and 2 (see paragraph 19)."*

   You have provided *in vitro* EpiOcular™ Eye Irritation Test (EIT) (i) conducted according to the OECD TG 492. The provided *in vitro* study (i) resulted in a positive prediction (mean tissue viability 28.4%), and you concluded that the Substance needs to be classified as irritating to eyes (Category 2 according to the CLP Regulation), although no self-classification for this endpoint was included in the IUCLID section 2.1 (GHS classification).

   As the mean tissue viability obtained was below the cut-off of 60% indicated for this test method, i.e. 28.4%, no conclusion can be made whether the Substance would merit Category 1 or 2 classification according to the CLP Regulation.

Therefore, the provided study does not fulfill the information requirement.

C. To fulfil an information requirement or be appropriate for an adaptation, a study must be reliable, i.e. assigned with a Klimisch score of 1 or 2 (ECHA Guidance R.4).

You have provided an *in vivo* eye irritation study (ii.) with the Klimish score 4 and with the explanation "secondary literature". You indicated that you consider this study as a key study for the current information requirement.

We agree that the Klimish score assigned by you is appropriate due to the following reasons:

- the study is not GLP compliant or conducted according to the relevant OECD Guideline;
- the severity of the effects (corneal injury) could not be assessed as no individual or mean irritation scores were provided; and
- the reversibility of the effects observed could not be established as the study contained only 24h observation period, and does not allow to make a conclusive decision whether the Substance would merit classification for serious eye damage (Category 1) or eye irritation (Category 2).

Due to these deficiencies that result in Klimish score 4, the provided study cannot be used to fulfil this information requirement.

In your comments to the draft decision you provided information on *in vitro* and *in vivo* studies conducted with analogue substances delta-dodecalactone, EC No. 211-932-4 (CAS No. 713-95-1) and omega-pentadecalactone, EC No. 203-354-6 (CAS No 106-02-5):

iii. Acute eye irritation/corrosion study according to the OECD TG 405 conducted with the delta-dodecalactone;
iv. An in vivo eye irritation/corrosion study (guideline not specified) conducted with the omega-pentadecalactone;
v. Reconstructed human Cornea-like Epithelium (RhCE) test according to the OECD TG 492 conducted with the delta-dodecalactone, and
vi. "Read-across justification for CAS no. 705-86-2".

We understand that you intend to use this information alongside the information from the studies on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

You have not provided a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

The sources of information must provide sufficient weight of evidence to conclude that the information requirement for serious eye damage or eye irritation, as specified in all of the available test guidelines (*in vitro* and *in vivo*[11]) are fulfilled by integrating and weighing the evidence.

Either in the registration dossier or referred to in your comments, you have provided information on five studies (i-v) addressing whether the substance causes damage to the eye.

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

D. Regarding the information provided in your registration dossier (i-ii), these sources of information have deficiencies affecting their reliability (see A, C above).

E. Regarding the information on similar substances submitted with your comments (studies iii-v), ECHA notes the following shortcomings with regards to the prediction of toxicological properties.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6 and related documents[2, 3].

Read-across hypothesis
A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[12]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the structural similarity and similarity in physico-chemical properties between the source substances and your Substance is a sufficient basis for predicting the properties of your Substance.

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

[11] OECD TGs 437, 438, 460, 491, 492 and 405
[12] ECHA Guidance R.6: QSARs and grouping of chemicals.

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

However, similarity in chemical structure and similarity of physicochemical properties does not necessarily lead to predictable or similar human health properties. You have not explained why the differences in the chemical structures should not influence the toxicological properties or should do so in a regular pattern. Therefore, a well-founded hypothesis to establish a reliable prediction for a serious eye damage or eye irritation, based on recognition of the structural differences between the source substance(s) and your Substance, is missing.

Adequacy and reliability of the information on the 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 should:

- 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); and
- 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.

In addition, Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including, among others, robust study summary(ies) of the source study(ies).[13]

A robust study summary must cover sufficient information to make an independent assessment of the study.[14]

In your comments to the draft decision, you have provided short descriptions of the source studies. However, you have not provided robust study summaries that allow independent assessment of the study.

In the absence of such documentation, ECHA cannot verify that the results to be read across meet the criteria above. The information on the analogue substances does therefore not provide reliable information for weight of evidence.

Based on the assessment above (A-E), your weight of evidence adaptation does not include any reliable sources of information to conclude on the property of the serious eye damage or eye irritation.

Integrating and weighing the evidence for eye irritation potential

In your comments to the draft decision, also relying on new information submitted with them, you propose that the *in vitro* study (i) indicating irritation to the eye is likely to provide a false positive results due to the lack of eye irritation demonstrated in the guideline *in vivo* study with the analogue substances (iii, iv). ECHA acknowledges that the information provided with the analogue substance indicate that the *in vitro* results (i and v) may be false positive. However, in the absence of reliable information (see point E above) allowing prediction of properties from the analogue substances, this cannot be confirmed.

[13] ECHA Guidance R.6, Section R.6.2.6.2
[14] How to report robust study summaries Practical Guide 3, Version 2.0 – November 2012

Accordingly, 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 for serious eye damage or eye irritation potential, as specified in all of the available test guidelines (*in vitro* and *in vivo*).

Conclusion on the weight of evidence
Your weight of evidence adaptation does not include any reliable source of information to conclude whether the substance causes serious eye damage or eye irritation. Therefore, your adaptation is rejected and additional information on addressing serious eye damage or eye irritation is needed.

To fulfil the information requirement for the Substance, to follow the testing strategy as outlined in the supplement to the OECD TG 405 is considered suitable.

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

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

According to the column 2 of Annex VII, Section 8.3.1, the *in vitro/in chemico* skin sensitisation test(s) do not need to be conducted if an *in vivo* study according to point 8.3.2 is available.

You have adapted the *in vitro/in chemico* skin sensitisation requirement (Annex VII, Section 8.3.1, column 2) and provided the following *in vivo* data and QSAR predictions (Annex VII, Section 8.3.2):

Key study:
i. Opdyke D. L. J., 1979 - Key study. A non-guideline human maximization test with the Substance.

Supporting studies:
ii. US Army Environmental Hygiene Agency, 1978 - Supporting study. A non-guideline guinea pig maximization test with the Substance.
iii. Danish Environmental Protection Agency (Q)SAR database study for the Substance, 2012 – Supporting study. (Q)SAR predictions for skin sensitisation in humans or guinea pigs estimated by four different models i.e., Battery, Leadscope, SciQSAR and CASE Ultra within Danish QSAR database.

We have evaluated the provided information and identified following issues:

A. To fulfil the information requirement, the study has to meet the requirements of OECD TG 406. Among others, the key parameters of this test guideline include:
   a) Concentration used for induction should be the highest to cause mild-to-moderate skin irritation and concentration used for challenge should be the highest non-irritant concentration;
   b) Adequate number of exposure (on day 0 intradermal induction, on day 6-8 topical induction and on day 20-22 challenge);
   c) Duration of topical induction (48 h) and challenge (24 h) exposures (challenge exposure should be performed after two week rest period); and

d) Use of adjuvant (Freunds Complete Adjuvant).

You have provided negative guinea pig maximisation test (ii.) conducted with the Substance.

In the reported data for the study ii. you have provided:
a) No information on dose level selection rational. A very low concentration (0.1%) was used for both induction and challenge without justification. The concentration used in the study did not cause mild-to-moderate irritation that is required for induction. There is no information available to assess the adequacy of the challenge concentration i.e. whether the concentration used is the highest non-irritating concentration;
b) Only one induction exposure;
c) No information has been provided on the timing of challenge exposure; and
d) No information on the use of adjuvant.

Therefore, the provided study does not cover the key parameters needed in an *in vivo* (OECD TG 406) study, and cannot be used to fulfil the information requirement.

B. To fulfil the information requirement, the study has to meet the general requirements for human studies. Among others, the key parameters of these studies includes[15]:
a) Information on the test protocol used (study design, controls);
b) Information on the extent of exposure (dose per square centimetre or concentration, frequency and duration);
c) Information on the presence of interfering factors (e.g. pre-existing dermal health effects, medication, presence of other skin sensitisers); and
d) Information on the health status of the exposed volunteers (the healthy worker effect).

You have provided negative human maximisation test (i.) conducted with the Substance.

In the reported data for the study (i.) you have provided:
a) No information on the study design was provided e.g. justification for dose level selection.
b) No information on the frequency or duration of the exposure.
c) No information on potential interfering factors.
d) No information on the health status of the exposed volunteers.

Therefore, the provided study does not cover the key parameters needed in human studies and cannot be used to fulfil the information requirement.

C. Qualitative or Quantitative structure activity relationship ((Q)SAR)) adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.3. are fulfilled.

You have provided (Q)SAR predictions for skin sensitisation (iii). However, as explained under General considerations , your (Q)SAR adaptation is rejected.

Therefore, it cannot be used to fulfill the information requirement.

D. To fulfil an information requirement or be appropriate for an adaptation, a study must be reliable, i.e. assigned with a Klimisch score of 1 or 2 (ECHA Guidance R.4).

[15] ECHA Guidance R.7a, Section R.7.3.5.2

You have provided studies with the following Klimisch scores:

i. Klimisch 2 with the following explanation: data from handbook or collection of data
ii. Klimisch 4 with the following explanation: secondary literature.

The following information, among others, is missing from the study (i.) to make an independent assessment of the study: detailed information on the study design used, and extent of exposure.

Therefore, the study cannot be considered as reliable with restrictions and it cannot be used to fulfill the information requirement.

For the study ii. ECHA agrees on the Klimish score 4 (not assignable) assigned by you. Therefore, it cannot be used to fulfill the information requirement.

Conclusion
Based on the assessment above, it is concluded that the information requirement is not fulfilled.

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

To fulfil the information requirement for the Substance, *in vitro/in chemico* skin sensitisation studies (OECD TG 442C, 442D and 442E) are considered suitable. In case the *in vitro/in chemico* methods are not suitable for the substance or the results cannot be used for classification and risk asssement an *in vivo* skin sensitisation study (OECD TG 429) must be performed.

4. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have adapted the standard information requirement according to Annex XI, Section 1.2. of of REACH (weight of evidence).

You have provided the following studies with the proposed analogue substances:

i. Ishidate et al., 1984, Bacterial reverse mutation assay (similar to OECD TG 471) conducted using ethyl butyrate, EC No. 203-306-4 (CAS No. 105-54-4); and
ii. Errol Zeiger 1985, Bacterial reverse mutation assay (similar to OECD TG 471) conducted using bis (2-ethylhexyl) adipate, EC No. 203-090-1 (CAS No. 103-23-1).

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on whether the Substance cause gene mutations in cultured bacteria.

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

The sources of information might provide sufficient weight of evidence to conclude that the information requirement for OECD TG 471 is fulfilled for the *in vitro* gene mutation study in bacteria if by integrating and weighing the evidence, e.g. the following aspects are covered:

- Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data must be provided on 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirement proposed to be adapted.

You have provided negative bacterial reverse mutation assays (similar to OECD TG 471) covering the following strains: *S. typhimurium* TA 92, TA 1535, TA 1537, TA 98, TA 94 and TA 100. Therefore, the sources of information (i) and (ii) provide some information on *in vitro* gene mutation in bacteria. However, the reported data for the studies did not include the appropriate 5 strains, as the information provided does not include results in the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

Therefore, the sources of information (i) and (ii) are only partly relevant for the (dangerous) property *in vitro* gene mutation in bacteria as investigated by OECD TG 471. The inclusion of the appropriate 5 strains is essential because the strains are specific for certain types of mutagens, and as specified in OECD TG 471, e.g. certain oxidising mutagens, cross-linking agents and hydrazines may be detected by *E.coli* WP2 strains or *S. typhimurium* TA102.

Additionally, while the sources of information (i) and (ii) provide partly relevant information on *in vitro* bacterial mutagenicity, these sources of information have the following deficiency affecting their reliability:

A. Read-across adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.5. are fulfilled.

The provided studies (i and ii) were conducted with proposed analogue substances. As explained under General considerations, your read-across approach is rejected. Therefore, the data is not considered reliable to conclude on *in vitro* bacterial mutagenicity.

Based on the assessment above, your weight of evidence adaptation does not include any reliable sources of information to conclude on the property *in vitro* gene mutation in bacteria.

Integrating and weighing the evidence for the dangerous property

Due to the deficiencies described above the partly relevant and unreliable sources of information does not address all of the information requirement and where the requirements are addressed it is done with high uncertainties, because those sources of information are unreliable. Therefore, when the information from various sources are assessed together, they give only low confidence (are of low total weight) compared to the information requirement. The information provided is only partly relevant as it does not cover all key investigations for *in vitro* gene mutation in bacteria (5^{th} strain), and is not reliable as it lacks details on read-across approach to allow verification that the properties of your Substance can be predicted from the data on the source substance(s).

Conclusion for weight of evidence adaptation
Based on the assessment 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 property foreseen to be investigated in an OECD TG 471 study. Your adaptation is rejected and the information requirement is not fulfilled.

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

5. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided a key study "*Short-term toxicity to aquatic invertebrates*" (2018) conducted according to OECD TG 202.

We have assessed this information and identified the following issue.

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

Based on the information in your dossier, the study you provided is not performed in compliance with GLP.

In your comments to the draft decision, you provide a short summary of the key study already addressed in the draft decision and you indicate that it fulfils all criteria in accordance with Annex XI, Section 1.1. We understand that you intend to use the key study to adapt this standard information requirement according to Annex XI, Section 1.1.2.

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

The provisions in Annex XI, Section 1.1 concern only data generated before REACH entered into application (June 2008).

As the key study is from the year 2018, Annex XI, section 1.1.2 does not apply. Therefore, your adaptation under Annex XI, Section 1.1.2. is rejected.

Furthermore, in your comments to the draft decision you refer to the following studies performed according to methods similar to OECD TG 202 with the two analogue substances selected using the OECD QSAR Toolbox (v 3.4):

i. A study with undecan-4-olide (CAS 104-67-6, EC 203-225-4); and
ii. A study with o-coumaric acid lactone (CAS 91-64-5, EC 202-086-7).

We understand that you intend to use this information alongside the information from the key study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

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

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

Relevance of information - requirement for a scientific justification for the use of information from similar substances

Based on the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

According to the information provided in your dossier, your WoE adaptation is based on information on similar substances obtained through the use of data from the QSAR Toolbox. You have provided a document in your comments to the draft decision (named [redacted]) detailing the structural and mechanistic criteria used for identifying the similar substances and providing high level information on the identity of these substances. However, these descriptions of structural and mechanistic criteria document the selection of the source substances but do not constitute on their own scientific justifications

on why this information is adequate and relevant in the context of this WoE approach.

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data[16,17]. However, no information on the applicability domain of the expert systems used to generate the alert profiles of the substances has been provided. Therefore the reliability of these predictions cannot be assessed.

Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as short-term toxicity to aquatic invertebrates, QSAR predictions alone do not establish that structurally similar substances have similar properties for this endpoint. You have not provided robust scientific information on why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance and which would include relevant and reliable studies of comparable design and duration establishing why the (eco)toxicological properties of the Substance can be determined from information on the similar substances Undecan-4-olide (CAS no. 104-67-6) and o-coumaric acid lactone (CAS no. 91-64-5). Therefore the information from studies (i) and (ii) is considered as not relevant for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified studies conducted with the similar substances undecan-4-olide (CAS no. 104-67-6) and o-coumaric acid lactone (CAS no. 91-64-5) that you intend to use as sources of information in your weight of evidence approach and you have provided high-level narratives presenting the studies with the above similar substances.

You have not provided robust study summaries for any of these source studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. In the absence of such information, we cannot assess the reliability of the information from studies (i) and (ii).

Requirement for documentation of the WoE adaptation

ECHA Guidance R.4.4 specifies that a WoE adaptation must involve an assessment of the relative values / weights of the several pieces of available information. This assessment must consider for instance the relevance and reliability of the information, the consistency of results/data, the nature and severity of effects. The lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion. The assessment should be documented and included in your technical dossier.

In the endpoint-specific section of your comments to the draft decision you describe the sources of information that you considered in your WoE adaptation and conclude that with this information you consider that you have been able to fulfil this information requirement.

Whilst this report can be regarded as integrated summary of the data set, you have not

[16] ECHA Guidance R.7a, Section R.7.6.4.1.2
[17] ECHA Guidance R.7a, Section R.7.5.4.1.1

communicated and documented in a robust and transparent manner your considerations on the relevance, relialibity of the individual sources of information, including how and why data from analogues can be relevant and reliable. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptation. Therefore your weight-of-evidence adaptation is not supported by adequate documentation.

Conclusion on the weight of evidence
As your WoE adaptation is neither based on relevant and/or reliable data to allow reaching a conclusion on the relevant hazard properties of the Substance nor supported by adequate documentation for the reasons presented above, it does not comply with the general rules of adaptation as set out in Annex XI, Section 1.2. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected.

Therefore, the information requirement is not fulfilled.

6. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study "*Toxicity to aquatic algae and cyanobacteria*" (2018) conducted according to OECD TG 201.

We have assessed this information and identified the following issues.

A. Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

   Based on the information in your dossier, the study you provided is not performed in compliance with GLP.

B. OECD TG 201 establishes the requirements for the data to be reported for a Growth inhibition study aquatic plants. The following is required (among other information):
   - adequate raw data relative to cell density determination to allow a verification that the validity criteria of the TG were fulfilled;
   - growth curves;
   - graphical presentation of the concentration/effect relationship;
   - estimates of toxicity for response variables including EC10 and NOEC.

   The provided robust study summary for the key study does not cover the elements listed above. Therefore, it is not possible to make an assessment of the study.

In your comments to the draft decision, you acknowledge the lack of information on the elements listed above. You provide a short summary of the key study already addressed in the draft decision and you indicate that it fulfils all criteria in accordance with Annex XI, Section 1.1. We understand that you intend to use the key study to adapt this standard information requirement according to Annex XI, Section 1.1.2.

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

The provisions in Annex XI, Section 1.1 concern only data generated before REACH entered into application (June 2008).

As the key study is from the year 2018, Annex XI, section 1.1.2 does not apply. Therefore, your adaptation under Annex XI, Section 1.1.2. is rejected.

Furthermore, in your comments to the draft decision you refer to the following additional studies:

i. A new study according to OECD TG 201 with the Substance;
ii. A study according to DIN 38412 part 9 with the analogue substance gamma-butyrolactone (CAS 96-48-0, EC 202-509-5) selected using the OECD QSAR Toolbox (v 3.4).

We understand that you intend to use this information alongside the information from the key study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

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

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

Relevance of information - requirement for a scientific justification for the use of information from similar substances

Based on the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

According to the information provided in your dossier, your WoE adaptation is based on information on a similar substance obtained through the use of data from the QSAR Toolbox. You have provided a document in your comments to the draft decision (named '[redacted]') detailing the structural and mechanistic criteria used for identifying the similar substance and providing high level information on the identity of this substance. However, these descriptions of structural and mechanistic criteria document the selection of the source substance but do not constitute on their own scientific justifications on

why this information is adequate and relevant in the context of this WoE approach.

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data[18,19]. No information on the applicability domain of the expert systems used to generate the alert profiles of the substance has been provided. Therefore the reliability of these predictions cannot be assessed.

Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as growth inhibition aquatic plants, QSAR predictions alone do not establish that structurally similar substances have similar properties for this endpoint. You have not provided robust scientific information on why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance and which would include relevant and reliable studies of comparable design and duration establishing why the (eco)toxicological properties of the Substance can be determined from information on the similar substance gamma–butyrolactone (CAS 96-48-0, EC 202-509-5). Therefore the information from study (ii) is considered as not relevant for this WoE adaptation.

Reliability of information

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified a new study with the Substance (study i) and a study conducted with the similar substance gamma–butyrolactone (CAS 96-48-0, EC 202-509-5) (study ii), which you intend to use as sources of information in your weight of evidence approach and you have provided high-level narratives presenting the studies.

You have not provided robust study summaries for these two studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. Furthermore, information is also missing to assess the key study, as already explained above. In the absence of such information, we cannot assess the reliability of the information from these studies.

Requirement for documentation of the WoE adaptation

ECHA Guidance R.4.4 specifies that a WoE adaptation must involve an assessment of the relative values / weights of the several pieces of available information. This assessment must consider for instance the relevance and reliability of the information, the consistency of results/data, the nature and severity of effects. The lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion. The assessment should be documented and included in your technical dossier.

In the endpoint-specific section of your comments to the draft decision you describe the sources of information that you considered in your WoE adaptation and conclude that with this information you consider that you have been able to fulfil this information requirement.

Whilst this report can be regarded as integrated summary of the data set, you have not

[18] ECHA Guidance R.7a, Section R.7.6.4.1.2
[19] ECHA Guidance R.7a, Section R.7.5.4.1.1

communicated and documented in a robust and transparent manner your considerations on the relevance, relialibity of the individual sources of information, including how and why data from analogues can be relevant and reliable. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptation. Therefore your weight-of-evidence adaptation is not supported by adequate documentation.

Conclusion on the weight of evidence

As your WoE adaptation is neither based on relevant and/or reliable data to allow reaching a conclusion on the relevant hazard properties of the Substance nor supported by adequate documentation for the reasons presented above, it does not comply with the general rules of adaptation as set out in Annex XI, Section 1.2. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected.

Therefore, the information requirement is not fulfilled.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. **Only if the results in Annex VII, Section 8.1. (request A.1.) are not adequate for classification and risk assessment, in vivo skin corrosion/irritation (Annex VIII, Section 8.1., column 2.; test method: OECD TG 404)**

In vivo skin corrosion/irritation study is a standard information requirement in Annex VIII of the REACH Regulation. Column 2 of Annex VIII, Section 8.1. provides that in case the *in vitro* study(ies) under Annex VII, Section 8.1.1 and 8.1.2 are not applicable for the substance, or the results are not adequate for classification and risk assessment, an *in vivo* study shall be considered.

The study records that you have provided for the skin corrosion/ irritation are rejected for the reasons provided in Appendix A, Section 1. It is also explained in that section why the information provided with your comments does not change ECHA's conclusions.

The result of the request for information in Appendix A., Section 1. will determine whether the present requirement for an *in vivo* skin corrosion/irritation study in accordance with Annex VIII, Section 8.1., column 2. is triggered. An *in vivo* skin corrosion/irritation is needed only if the results in Annex VII, Section 8.1. are not adequate for classification and risk assessment.

When considering the results obtained from the *in vitro* study/ies, it is important to consider whether a specific conclusion on classification according to CLP regulation can be made based on the results, i.e. interpretation of the results and prediction model of a particular test method[20].

2. **Only if the results in Annex VII, Section 8.2. (request A.2.) are not adequate for classification and risk assessment, in vivo serious eye damage/eye irritation (Annex VIII, Section 8.2., column 2.; test method: OECD TG 405) with the Substance**

In vivo eye irritation is a standard information requirement in Annex VIII of the REACH Regulation. Column 2 of Annex VIII, Section 8.2. provides that in case the *in vitro* study(ies) under Annex VII, Section 8.2.1. are not applicable for the substance, or the results are not adequate for classification and risk assessment, an *in vivo* study shall be considered.

The study records that you have provided for the eye damage/eye irritation are rejected for the reasons provided under request A.2 above. It is also explained in that section why the information provided with your comments does not change ECHA's conclusions.

The result of the request for information under request A.2 above will determine whether the present requirement for an *in vivo* serious eye damage/eye irritation study in accordance with Annex VIII, Section 8.2., column 2. is triggered. An *in vivo* serious eye damage/eye irritation is needed only if the results in Annex VII, Section 8.2. are not adequate for classification and risk assessment.

[20] ECHA Guidance R.7a, Section R.7.2.4

When considering the results obtained from the *in vitro* study/ies, it is important to consider whether a specific conclusion on classification according to CLP regulation can be made based on the results i.e. interpretation of the results and prediction model of a particular test method[21].

3. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An *in vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have adapted the standard information requirement according to Annex XI, Section 1.2. Weight of evidence of REACH.

You have provided the following studies with the analogue substances:

i. Ishidate et al., 1984 – *In Vitro* Mammalian Chromosome Aberration Test in Chinese hamster fibroblast cell line (similar to OECD Guideline 473) conducted using ethyl butyrate, EC No 203-306-4;
ii. Ishidate et al., 1984 – *In Vitro* Mammalian Chromosome Aberration Test in Chinese hamster fibroblast cell line (similar to OECD Guideline 473) conducted using decanal, EC No. 203-957-4 (CAS No. 112-31-2);

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the Substance does not cause chromosomal aberrations in cultured mammalian cells.

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

[21] ECHA Guidance R.7a, Section R.7.2.8

The sources of information might provide sufficient weight of evidence to conclude that the information requirement for OECD TG 473 or OECD TG 487 is fulfilled for the *in vitro* cytogenicity study or *in vitro* micronucleus study, respectively, if by integrating and weighing the evidence, e.g. the following aspect is covered:

- Detection and quantification of chromosomal aberrations (OECD TG 473) or micronuclei (OECD TG 487) in cultured mammalian cells.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on this property as investigated in the information requirement proposed to be adapted.

The reported data for the studies (i-ii) provide some relevant information on *in vitro* chromosomal aberration as investigated by OECD TG 473 study. However, the sources of information have the following deficiencies affecting their reliability:

A. Read-across adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.5. are fulfilled.

   The provided studies (i. and ii.) were conducted with proposed analogue substances. As explained under General considerations, your read-across approach is rejected. Therefore, the data is not considered reliable to conclude on *in vitro* chromosomal aberration.

B. To fulfil the information requirement, a study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[22]. The key parameters of the OECD TG 473 include:
   a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation;
   b) At least 300 well-spread metaphases must be scored per concentration; and
   c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.

   You have provided *in vitro* mammalian chromosome aberration tests similar to OECD Guideline 473 (studies i-ii).

   However, the reported data for the studies has the following deficiencies:

   Both in study (i) and (ii) only 100 well-spread metaphases were scored per concentration. In addition, details for positive controls were not specified and therefore, no conclusion can be made for these key parameters.

   Further to this, study (ii) was conducted in absence of metabolic activation. In addition, the test conditions were not specified for study (i) and therefore, no conclusion can be made for this key parameter.

To conclude, the reported data for the studies you have provided did not cover two separate test conditions, scoring of at least 300 metaphases per concentration, or positive control(s) as required by OECD TG 473. Therefore, the information provided for studies (i. and ii.) does not cover key parameter(s) required by OECD TG 473. The inclusion of two separate conditions, with and without exogenous metabolising system is important because the mutagenic potential of certain substances is dependent on metabolic activation. In addition,

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

the examination of at least 300 metaphases per concentration is critical for the statistical power of the study. Therefore, the provided studies cannot be considered as reliable sources of information that could contribute to the conclusion on *in vitro* chromosomal aberration.

Based on the assessment above, your weight of evidence adaptation does not include any reliable sources of information to conclude on the property *in vitro* chromosome aberrations in mammalian cells.

Integrating and weighing the evidence for the dangerous property

Due to the deficiencies described above the partly relevant and unreliable sources of information does not address all the information requirement and where the requirements are addressed it is done with high uncertainties as those sources of information are unreliable. Therefore, when the information from various sources are assessed together, they give only low confidence (are of low total weight) compared to the information requirement. The provided information is not reliable as it lacks details on read-across approach to allow verification that the properties of your Substance can be predicted from the data on the source substance(s) and does not cover key parameters of OECD TG 473.

Conclusion for weight of evidence adaptation
Based on the assessment 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 property foreseen to be investigated in an OECD TG 473/487 studies. Your adaptation is rejected and the information requirement is not fulfilled.

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

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

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided a key study "*Short-term toxicity to fish*" (2018) conducted according to OECD TG 203.

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP, Directive 2004/10/EC) or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

Based on the information in your dossier, the study you provided is not performed in compliance with GLP.

In your comments to the draft decision, you provide a short summary of the key study already addressed in the draft decision and you indicate that it fulfils all criteria in accordance with

Annex XI, Section 1.1. We understand that you intend to use the key study to adapt this standard information requirement according to Annex XI, Section 1.1.2.

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

The provisions in Annex XI, Section 1.1 concern only data generated before REACH entered into application (June 2008).

As the key study is from the year 2018, Annex XI, section 1.1.2 does not apply. Therefore, your adaptation under Annex XI, Section 1.1.2. is rejected.

Furthermore, in your comments to the draft decision you refer to the following study performed with an analogue substance selected using the OECD QSAR Toolbox (v 3.4):

i. A study according to OECD TG 203 with 4-methyleneoxetan-2-one (CAS 674-82-8, EC 211-617-2).

We understand that you intend to use this information alongside the information from the key study on the Substance included in your dossier as part of a weight of evidence adaptation according to Annex XI, Section 1.2.

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

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.4.4, 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 of the information for the given regulatory endpoint. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

Relevance of information - requirement for a scientific justification for the use of information from similar substances

Based on the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

According to the information provided in your dossier, your WoE adaptation is based on information on a similar substance obtained through the use of data from the QSAR Toolbox. You have provided a document in your comments to the draft decision (named '[redacted]') detailing the structural and mechanistic criteria used for identifying the similar substance and providing high level information on the identity of this

substance. However, these descriptions of structural and mechanistic criteria document the selection of the source substance but do not constitute on their own scientific justifications on why this information is adequate and relevant in the context of this WoE approach.

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data[23,24]. No information on the applicability domain of the expert systems used to generate the alert profiles of the substances has been provided. Therefore the reliability of these predictions cannot be assessed.

Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as short-term toxicity to fish, QSAR predictions alone do not establish that structurally similar substances have similar properties for this endpoint. You have not provided robust scientific information on why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance and which would include relevant and reliable studies of comparable design and duration establishing why the (eco)toxicological properties of the Substance can be determined from information on the similar substance 4-methyleneoxetan-2-one (CAS 674-82-8, EC 211-617-2). Therefore the information from study (i) is considered as not relevant for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified a study conducted with the similar substance 4-methyleneoxetan-2-one (CAS 674-82-8, EC 211-617-2) that you intend to use as source of information in your weight of evidence approach and you have provided high-level narratives presenting the study with the above similar substance.

You have not provided a robust study summary for the source study. In particular you have not provided detailed information on the methods, results and conclusions of this study allowing for an independent assessment of the study. In the absence of such information, we cannot assess the reliability of the information from study (i).

Requirement for documentation of the WoE adaptation

ECHA Guidance R.4.4 specifies that a WoE adaptation must involve an assessment of the relative values / weights of the several pieces of available information. This assessment must consider for instance the relevance and reliability of the information, the consistency of results/data, the nature and severity of effects. The lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion. The assessment should be documented and included in your technical dossier.

In the endpoint-specific section of your comments to the draft decision you describe the sources of information that you considered in your WoE adaptation and conclude that with this information you consider that you have been able to fulfil this information requirement.

[23] ECHA Guidance R.7a, Section R.7.6.4.1.2
[24] ECHA Guidance R.7a, Section R.7.5.4.1.1

Whilst this report can be regarded as integrated summary of the data set, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, relialibity of the individual sources of information, including how and why data from analogues can be relevant and reliable. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptation. Therefore your weight-of-evidence adaptation is not supported by adequate documentation.

Conclusion on the weight of evidence

As your WoE adaptation is neither based on relevant and/or reliable data to allow reaching a conclusion on the relevant hazard properties of the Substance nor supported by adequate documentation for the reasons presented above, it does not comply with the general rules of adaptation as set out in Annex XI, Section 1.2. Therefore, your adaptation according to Annex XI, Section 1.2. is rejected.

Therefore, the information requirement is not fulfilled.

Appendix C: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 16 January 2019.

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.

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: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   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: 'How to report robust study summaries'[25].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[26].

[25] https://echa.europa.eu/practical-guides
[26] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[27]

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[28]

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.

OECD Guidance documents[29]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD 43.

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

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.