~~Confidential~~

Helsinki, 21 October 2021

Addressees
Registrant(s) of JS_IFF_Cyclacet as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
22/03/2019

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of 3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-yl acetate and 3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-6-yl acetate
EC number: 911-369-0
CAS number: NS

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***27 July 2023***.

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

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

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)
2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)
3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)
4. Long-term toxicity testing on terrestrial invertebrates (triggered by Annex IX, Section 9.4.1., column 2; test method: OECD TG 222 or 220 or 232)
5. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216)
6. Long-term toxicity to terrestrial plants (triggered by Annex IX, Section 9.4.3., column 2; test method: OECD TG 208 with at least six species or ISO 22030)

Reasons for the request(s) are explained in the following appendices:
- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes IX of REACH", respectively.

Information required depends on your tonnage band
You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

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

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

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

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

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

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

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

Appendix on Reasons common to several requests

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

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

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)
- Long-term toxicity testing on terrestrial invertebrates (Annex IX, Section 9.4.1., column 2)
- Effects on soil micro-organisms (Annex IX, Section 9.4.2.)
- Long-term toxicity to terrestrial plants (Annex IX, Section 9.4.3., column 2).

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

Grouping of substances and read-across approach

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions of (eco)toxicological properties

You have provided the following read-across hypothesis common for the prediction of toxicological properties : *"Cyclacet has the same developmental toxicity as Verdox".*

You have provided the following read-across hypothesis for the prediction of the long-term toxicity to fish and aquatic invertebrates, and of the toxicity to soil organisms: *"Cyclacet has similar chronic fish and Daphnia toxicity compared to Cyclaprop after conversion" and "Cyclacet's terrestrial EC10/NOEC values can be derived from Verdox after conversion using molecular weight and log Kow"*, respectively.

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have similar properties.

The toxicological properties of your Substance are predicted to be quantitatively equal to

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

those of the source substance. The toxicity to soil organisms and the long-term toxicity to fish and aquatic invertebrates for your Substance are predicted by conversion of respective effect concentrations of the source substances, i.e. are based on an identified "trend".

You intend to predict the properties for the Substance, as target substance, from information obtained from the following source substances:

a) "Verdox", 2-tert-butylcyclohexyl acetate, EC No. 243-718-1:
   - Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
   - Long-term toxicity testing on terrestrial invertebrates (Annex IX, Section 9.4.1., column 2)
   - Effects on soil micro-organisms (Annex IX, Section 9.4.2.)
   - Long-term toxicity to terrestrial plants (Annex IX, Section 9.4.3., column 2);
b) "Cyclaprop", 3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-indenyl propionate, EC No. 272-805-7, CAS No. 68912-13-0:
   - Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
   - Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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

1. Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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).

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 source substance(s) and your Substance[5]. 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.

a. Pre-natal developmental toxicity

Your read-across hypothesis is that the similarity in chemical structure and in some of the toxicological properties between the source substance Verdox and your Substance is a sufficient basis for predicting the properties of your Substance for other endpoints.

In the CSR you explain with regard to structural similarity and differences: *"Cyclacet and Verdox have a similar* [redacted]. *Absorption via all routes will be similar in view of similar appearance, molecular weights and physico-chemical parameters. The lower water solubility and higher log Kow of Verdox compared to Cyclacet will not make a difference in absorption because it is still in the range for good oral absorption (*[redacted]*, 2002)."*

[5] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.

The Substance is an [redacted], whereas the source substance is an [redacted]. There is no further explanation how the differences in structural features between the Substance and the source substance impact the prediction of properties; in particular the:

- [redacted], which is structurally more rigid compared to the [redacted];
- effect on the 3D-structure/potential receptor-binding properties of the Substance by the [redacted];
- presence of [redacted] of the Substance and their impact on the 3D-shape;
- effect of the [redacted] on metabolism other than hydrolysis of the [redacted].

In your justification you have not adressed how properties of the Substance, which may result from the specific 3D shape of the [redacted], can be predicted from the source substance. The source substance's substructure has more degrees of freedom in how its (receptor-specific) 3D shape is formed. This may be relevant for the prediction of several (eco)toxicological properties which rely on differences in metabolism of a substance, and it is particularly important in the prediction of pre-natal developmental toxicity, which investigates the effect of a substance on receptors and targets of developing embryos and fetuses.

In your comments on the initial draft decision you describe similarities and differences in the chemical structure and their (assumed) effect(s) on the prediction of properties from the source to the target substance. ECHA has assessed the relevance of similarities in different subsections of this appendix. You indicate dissimilarities relevant to the prediction of pre-natal developmental toxicity as:

i. *"The Cyclacet [redacted] is slightly more rigid compared to [redacted] of Verdox, the flexibility of Verdox is reduced by the [redacted].*
ii. *The [redacted] Cyclacet are all in the [redacted] with no effect on lipophilicity. Therefore, the [redacted] are expected to have similar sensitivity considering receptor binding for lipophilicity.*
iii. *Both [redacted] are considered to be resistant to further metabolic attack, including the [redacted], which does not show any oxidation reactivity in e.g. mutagenicity testing."*

You claim that these dissimilarities result in "*similar receptor-binding and/or receptor-blocking activities".* You have not provided further (experimental) information with your comments on the initial draft decision, in support of your claims i., ii. and iii. Therefore these remain unsupported hypotheses instead of justifications.

b. Toxicity to soil organisms

Your read-across hypothesis is that the similarity between chemical structures, similar bioavailability and presence of the same functional group ([redacted]) leading to the same toxicity mode of action between the source substance Verdox and your Substance is a sufficient basis for predicting the properties of your Substance for these endpoints.

In the registration dossier, including CSR you explain following:
"*Structural similarities and differences: Cyclacet and Verdox have a similar [redacted]. The difference is that Cyclacet has [redacted], while Verdox has a [redacted].*

Bioavailability: Cyclacet (target) and Verdox (source) have somewhat similar bioavailability based on the similarity in chemical structure and molecular weight Cyclacet, the lower log Kow of Cyclacet compared to Verdox is not too different to present a difference in bioavailability.
Mode of action (MoA): Cyclacet and Verdox have both the same a [redacted] and therefore the MoA is the same based on the same [redacted]. The difference in log Kow between Cyclacet and Verdox 3.9 and 4.75 are accounted for when deriving the terrestrial toxicity values for Cyclacet as presented in Table 1 using the following equation: (Log NOEC/EC10 target (mmol) = Log NOEC/EC10 source (mmol) x log Kow source/Log Kow target)."

As explained in the section for pre-natal developmental toxicity above, there is no further explanation how the differences in structural features between the Substance and the source substance Verdox impact the prediction of the specific property toxicity to soil organisms. Furthermore, the specific mode of toxicity action to soil organisms for the Substance and source substance Verdox is not specified and it is not explained how structural differences between these two substances were considered to conclude on the "same" mode of toxicity action to soil organisms.

c. Conclusion on the read-across hypothesis

Thus, as described above, the structural similarities and differences between the source substance Verdox and your Substance need to be recognised in a well-founded justification to establish a reliable prediction for (eco)toxicological properties, but this is not the case here.

2. Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[6]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s). Supporting information must include supporting information such as bridging studies to compare properties of the Substance and source substance(s).

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

a. Pre-natal developmental toxicity

You have provided a screening for reproductive/developmental toxicity study (OECD TG 421, 2010) with the Substance and a pre-natal developmental toxicity study (OECD TG 414) in a first species with the source substance Verdox. Furthermore, you have provided a comparison of study results for repeated dose toxicity between the Substance and the source substance in the CSR (OECD TG 408), without providing robust study summaries in the technical dossier (IUCLID).

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

In your comments on the initial draft decision, you have provided full study reports for the two 90-day studies (OECD TG 408) performed with the target- (2013) and the source substance (2017), as well as for the combined repeated dose toxicity and screening for toxicity to reproduction/ development study (OECD TG 422) with the source substance (2012).

ECHA observes several deficiencies with regard to the supporting information for the comparison of effects by the Substance and the source substance:

1) An absence of effects for developmental toxicity *post* parturition in the screening study does not allow to conclude on similar human health properties in a *pre*-natal developmental toxicity study.
2) In addition to similar effects such as kidney effects in male rats, which you consider as specific to male rats and not relevant to humans, the provided screening for reproductive/developmental toxicity study (OECD TG 421, 2010) and repeated dose toxicity studies indicate differences in toxicological profiles between the Substance and the source substance. Adrenal effects confirmed by histopathology have been observed only with the Substance, while relative uterus weights were increased up to 77% only with the source substance in the high dose group of a 90-day repeated dose toxicity study (OECD TG 408).
3) Furthermore, the dosing in the source study (OECD TG 414, 2017) does not meet the criteria of the OECD test guideline as explained in *Appendix A Section A.1* and therefore it cannot be excluded that effects would have been observed with appropriate dosing. Thus this source study is considered to be invalid and cannot be used for comparison of effects.

In your comments on the initial draft decision, you provide a comparison of properties of the source- and target substance as predicted by the OECD QSAR toolbox. Such a comparison may serve to differentiate those source substances, which are obviously unsuitable for a prediction of the target substance's properties, from source substances which may be worth further consideration. However, QSAR toolbox predictions contain a limited set of high-level predictions and by no means offer detailed comparisons between the multitude of receptors which are relevant to pre-natal developmental toxicity; and to a large extent not identified for use in the toolbox. Therefore they cannot be used to predict the hazard property in question. Furthermore, the toolbox indicates low structural similarity between target- and source substance as reported in your comments on the initial draft decision.

In your comments you further explain that "*The differences* in toxicity profiles between source- and target substance observed by ECHA (2, above) *are attributed to chance because these were only found in one study*". ECHA disagrees because the findings occured in a modern study with a certain statistical power due to the size of the animal groups, which was conducted according to OECD TG 421 and is fully reliable. Furthermore it is the only such study to have investigated the Substance's effect on the organs in question. The study report you provided "on the Substance" (OECD TG 408, 2013) has been conducted with Acetoxy-dihydrodicyclopentadiene (CAS 54830-99-8), according to the substance identifiers in the study report. ECHA observes that this substance is not the Substance[7], but instead a close analogue for which you have not provided any read-across adaptation. The structural difference is manifest in the location of the double bond. In the source substance it is [redacted], whereas in the target it is located [redacted].

b. Toxicity to soil and aquatic organisms

[7] According to information from Section 1.2 of your technical dossier: "*NMR analysis indicates Cyclacet is a* [redacted]. *The proton NMR data indicates Cyclacet is a* [redacted] *as evidenced by the area for the two main signals.*"

You have provided the read-across hypothesis for the prediction of the long-term aquatic toxicity and prediction of toxicity to soil organisms which qualitatively assumes that different compounds have similar properties. Quantitatively you have estimated long-term aquatic toxicity and toxicity to soil organisms effect concentrations for the Substance by applying conversion factors (estimated based on acute-to-chronic toxicity ratio and/or based on differences in physico-chemical parameters) to the respective effect concentrations of source substances, i.e. Cyclaprop for long-term aquatic toxicity and Verdox for toxicity to soil organisms.

Furthermore, in the registration dossier, including CSR, you have noted that "*For Cyclacet no terrestrial toxicity information is available, but for the related analogue Verdox long-term terrestrial toxicity is available and read across can be applied.*"

You have applied an analogue approach and, by using conversion factors, you have quantitatively estimated the effects values for long-term aquatic toxicity and for toxicity to soil organisms of the Substance, i.e. referring to ECHA Guidance R.6, Section R.6.2.2.1 (p. 81-82) you have used an option of using an internal QSAR assuming that predicted properties follow some specific trend. However, in case of analogue approach, the grouping is based on a very limited number of chemicals, where trends in properties are not apparent. In particular, if there is only one source substance, it is not possible to establish trends for the predicted property because it relies on too few source studies. Thus, for an analogue approach quantitative estimations based on a trend are not possible and your applied option of an internal QSAR only applies when more than one source substance is available.

In your comments on the initial draft decision, in respect of the read-across approach proposed for long-term aquatic toxicity you note that you have generated further data on acute and chronic toxicity to aquatic invertebrates for another '*cycla ester'*, being Cyclabute (EC No. 916-331-7) as well as a full acute and chronic aquatic toxicity dataset is available for Cyclaprop. You propose to follow a group approach for the three cycla-esters (the Substance, Cyclaprop and Cyclabute) by showing that the short- and long-term aquatic toxicity follow a Kow dependant trend and hypothesise that based on this trend "*Cyclacet has lower chronic fish and Daphnia toxicity (higher L(E)C values) compared to Cyclaprop and Cyclabute*". You note that based on the structural similarity including presence of the same [redacted] the members of the group would have the same mode of action in fish, invertebrates and algae for both short- and long-term toxicity. You note that newly conducted long-term toxicity study with aquatic invertebrates is considered as a bridging study for predicting long-term aquatic toxicity of the Substance. Based on all these considerations you summarise that "*Cyclacet's long-term toxicity for fish and Daphnia can be predicted from Cyclaprop and Cyclabute by converting their values using molecular weight and log Kow differences*" and "*This grouping approach will be presented in an update of the Cyclacet and Cyclabute dossier*".

As explained in ECHA Guidance R.6 (section R.6.2.2.1):

- when applying quantitative read-across, there are four general ways of estimating the missing data point:
  - A) by using the endpoint value of a source chemical, e.g. the closest analogue in a (sub)category;
  - B) by using an internal QSAR to scale the available experimental results from two or more source chemicals to the target chemical;
  - C) by processing the endpoint values from two or more source chemicals (e.g. by averaging, by taking the most representative value);
  - D) by taking the most conservative value of the closest analogues or the most conservative value in the (sub)category.

The Substance is at a structural border of the proposed category of 3 substances. As explained in a ECHA Guidance, R.6, in general, interpolation between category members is preferred to extrapolation. Consistent trend in the behaviour of a group of chemicals should be demonstrated for a dependency between predicted property and physico-chemical parameter used as a basis for such prediction.

It is not possible to demonstrate consistent trend based on two data points only when extrapolation outside of the established trend is used to predict the property for the Substance which is at the border of the proposed category.

Therefore your quantitative estimation of long-term aquatic toxicity and toxicity to soil organisms effect concentrations for the Substance by conversion from the source substances is not acceptable. However, applicability of other ways of quantitative read-across listed under A, C, D bullet-points above should be considered if relevant.

Furthermore, the data set reported in the technical dossier does not include relevant, reliable and adequate information, for example, from bridging studies of comparable design and duration for the Substance, to support your read-across hypothesis for the toxicity to soil organisms.

Finally, in accordance with Annex XI, Section 1.5., if grouping concept is applied then in all cases the results should be adequate for the purpose of classification and labelling and/or risk assessment. Therefore, the studies with source substances should be conducted with the corresponding test methods referred to in Article 13(3) and key conditions of these test methods should be fulfilled.

Adequacy and reliability of the long-term toxicity study with aquatic invertebrates with Cyclaprop is addressed below in Appendix A, section 2. Furthermore, if the grouping and read-across adaptation is applied to adapt standard information requirements for the long-term aquatic toxicity and Cyclabute is used as source substance, the adequate information with the Cyclabute should be submitted in an updated registration dossier by the deadline set out in the decision.

c. Conclusion on supporting information

Thus, based on these observations, you have not established that the Substance and the source substances Verdox and Cyclaprop are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

B. Conclusions on the read-across approach

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

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

1. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a pre-natal developmental toxicity study (OECD TG 414) with an analogue substance.

As explained in the Appendix on general considerations your adaptation is rejected. In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3). In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include e.g.

- highest dose level should aim to induce some developmental and/or maternal toxicity.

  You have justified the lower dose levels used in the OECD TG 414 study based on data obtained from a 14-day dose-range finding study (OECD TG 422) with the source substance. You concluded that "*the reduced food intake and the accompanying lower body weights in the high-dose group are considered to be due to reduced palatability rather than to the test substance per se, and are not considered to be adverse*", and "*the 7500 mg/kg diet* [= 444 mg/kg bw/d] *was sufficiently high to present* (absence of adverse) *effects for the OECD TG 414 study.*"

The highest dose level in the study did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity. ECHA does not consider the non-adverse liver effects observed in male rats only in the OECD 422 study, relevant for a dose selection for the OECD 414 for pregnant females.

Furthermore, the pre-natal developmental toxicity study was conducted via feed despite the known issues with the palatability of the test material, which was observed in the 14-days dose range finding study and was attributed to the odorous character of the test material. You have not justified in your dossier why dosing via gavage was not performed to overcome the known palatability issues.

In your comments on the initial draft decision you explain that

- you wanted to avoid *"overloading the metabolic pathway, causing peak levels in the systemic circulation for which animals but more specifically fetuses may be vulnerable", a*nd
- *"Because all previous studies were done via diet, also the OECD TG 414 was done via the diet to be able to compare the results with the other dietary studies."*

ECHA observes that at least one study (OECD TG 421, 2010) was conducted via gavage instead of dietary exposure, with a top dose of 1000 mg/kg bw/d; a further dietary study (OECD TG 408, 2012) was tested up to 1500 mg/kg bw/d. Since these studies concluded the

NOAEL at the top dose in the absence of adverse effects, testing below the limit dose would not fulfil the requirements of the OECD test guidelines on the choice of top dose. ECHA concludes that future studies via gavage can be compared to at least one existing study via the same route and type of administration. Furthermore it is possible to achieve and exceed the limit dose specified by OECD TG 414 that is the subject of this request. ECHA considers that the requested study investigates intrinsic properties of the Substance for the purpose of hazard identification. This includes the metabolism of the test material at doses up to the limit dose, irrespective of whether this investigation is for your Substance or any other substance.

Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in OECD TG 414.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[8] administration of the Substance.

2. Long-term toxicity testing on aquatic invertebrates

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a long-term toxicity study on aquatic invertebrates (OECD TG 211) with an analogue substance.

As explained in the Appendix on reasons common to several requests your adaptation is rejected.

In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3). To fulfil the information requirement, a study must comply with the OECD TG 211. Therefore, the following requirements must be met:

For a test to be valid, the following performance criteria should be met in the controls:

- the percentage of mortality of the parent animals (female *Daphnia*) is ≤ 20% at the end of the test;
- the mean number of living offspring produced per parent animal surviving is ≥ 60 at the end of the test;

- if at the end of the test the deviation from the nominal or measured initial concentration is greater than ± 20%, results should be expressed in terms of the time-weighted mean;
- for flow-through tests, ≥ 20 animals are used at each test concentration. Test animals are divided into two or more replicates with an equal number of animals;
- the test medium fulfils the following condition(s): total organic carbon (TOC) ≤ 2 mg/L.

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

The following has been reported in the dossier:

- "*Parental mortality was 25% in solvent control (exceeding the 20%). In the lowest test concentration no immobility was observed and therefore this deviation is considered not have affected the results.*";
- for the nominal concentrations 0.33 mg/l and 9.0 mg/l at the end of the test the deviation from the measured initial concentration is greater than ± 20%;
- the test was conducted under flow-through conditions and the number of test animals was 10 per test concentration;
- water from the "*well located 40 meters deep on the Wildlife International Ltd. Site*" was used for the preparation of test medium and TOC concentration in the test medium is not reported.

One of validity criteria is not fulfilled, as mortality of the parent animals in the solvent control was above 20%. Your justification on why observed parental mortalities in solvent control should be disregarded is not acceptable, because for the results interpretation and estimation of (no-)effect concentrations results of solvent control should be disregarded and 0% mortality in the lowest test concentration should be compared with parental mortalities in other test concentrations for determination of statistical significance of observed effect. However you have not demonstrated this and therefore, your justification on why such deviation should not be considered is not acceptable.

In your comments on the initial draft decision, you explain that the immobility of 25% of organisms detected in the solvent "*In view of the immobility of the control and lower test concentrations not exceeding the 10% this was considered not affecting the final study results*".

In the registration dossier for the determination of (no-)effect concentrations for the parental mortality you note that statistical analysis is based on the comparison of results of treatment groups with the solvent control. Thus, you propose to disregard the results of high parental mortality in the solvent control, however consider these results when estimate (no-)effect concentrations for the parental mortality. Therefore, as explained above, if you disregard the results of parental mortality in solvent control, estimation of (no-)effect concentrations should be based on the comparison to 0% parental mortality detected in the lowest test concentration and not on the comparison to 25% parental mortality detected in the solvent control.

In your comments on the initial draft decision, you note that "*Despite the use of the solvent, slight oily material was seen with increasing concentration. In view of the measured concentration be within 20% of the nominal this is not considered to have affected the final study results*".

In the registration dossier for nominal exposure concentration of:

- 0.33 mg/l you report initial measured concentration of 0.342 mg/l and concentration of 0.238 mg/l after 21 day, i.e. app. 70% of initial measured concentration was detected.
- 9 mg/l you report initial measured concentration of 8.66 mg/l and concentration of 6.80 mg/l after 7 day, i.e. app. 78.5% of initial measured concentration was detected.

For the nominal exposure concentrations of 0.33 mg/l and 9.0 mg/l time-weighted mean concentrations should be estimated and used for the estimation of (no-)effect concentrations. However, this was not done.

The requirement on the number of test animals per test concentration is not fulfilled.

Finally, there is no information on the TOC concentration in the test medium. Therefore, you have not demonstrated compliance with the above conditions.

Thus, the requirements of OECD TG 211 are not met.

Furthermore, in your comments on the initial draft decision you note that according to Annex IX of the REACH Regulation long-term aquatic toxicity information is triggered by the outcome of risk assessment and as the Substance is not classified for any of the hazard categories, "*an exposure assessment and risk assessment are not needed and therefore no need is identified to generate further long-term aquatic toxicity data for Cyclacet*".

As noted above long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.) and compliance of the registration dossier with this standard information requirement was performed against the requirements applicable to the adaptation according to Annex XI, Section 1.5 provided in your registration dossier. In respect of the argument that the long-term aquatic toxicity information is triggered by the outcome of risk assessment, Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish and aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish and aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018). Furthermore, results of the long-term aquatic toxicity studies itself can lead to the classification of the Substance as hazardous to aquatic organisms and identify hazards to aquatic organisms which would need to be addressed in the exposure assessment and risk characterisation in line with requirements of Article 14 and Annex I of REACH.

On this basis, the information requirement is not fulfilled.

3. Long-term toxicity testing on fish

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a long-term toxicity study on fish (OECD TG 210) with an analogue substance.

As explained in the Appendix on reasons common to several requests your adaptation is rejected.

In your comments on the initial draft decision, you provide the same comments as for the Long-term toxicity testing on aquatic invertebrates which are addressed in the Appendix A, section 2 and Appendix on Reasons common to several requests above.

On this basis, the information requirement is not fulfilled.

Study design

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

4. Long-term toxicity on terrestial invertebrates

Short-term toxicity testing on invertebrates is an information requirement under Annex IX to REACH (Section 9.4.1.). Long-term toxicity testing on invertebrates must be considered

(Section 9.4., Column 2) if the substance has a high potential to adsorb to soil or is very persistent.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a long-term toxicity study on invertebrates (OECD TG 222) with an analogue substance.

Based on the information provided in the registration dossier, the Substance is not readily biodegradable (10% degradation after 28 days in key study according to OECD TG 301F) and there is no half-life of the Substance in soil available, therefore the Substance is considered to be very persistent (ECHA Guidance R.7c). Thus, the long-term toxicity testing on terrestrial organisms is required.

As explained in the Appendix on reasons common to several requests your adaptation is rejected.

In your comments on the initial draft decision, you note that:

- These studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely.
- In the absence of toxicity data for soil organisms, the equilibrium partitioning method may be applied to assess the hazard to soil organisms.
- The choice of the appropriate tests depends on the outcome of the chemical safety assessment.
- In particular for substances that have a high potential to adsorb to soil or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term.

You note that the Substance is not classified for any human health or environmental hazard classes or categories and therefore there is no need to perform an exposure assessment and chemical safety assessment, i.e. you "*consider that this implicitly means that there is no trigger because of the (absence of a) chemical safety assessment to conduct further testing for the terrestrial compartment*".

You note that you agree that the PNEC derivation for the terrestrial compartment, which is part of hazard assessment, needs to be conducted, but this can be done through the Equilibrium Partitioning Method. You consider that for the Substance "*based on non-persistency in the aquatic compartment, soil Hazard class 1 is applicable*". You base such conclusion on information from similar Cycla esters (Cyclabute). These substances will degrade significantly in the aquatic compartment to Cycla-alcohol and less so the ketone forms with a half-life of around 17 days at 12°C meaning that these materials should not be regarded as persistent or very persistent in the aquatic compartment.

Furthermore, you note that direct exposure of the soil compartment is not expected and that based on modelling of the fate of the Substance in waste water treatment plant "*will mainly partition to the aquatic compartment (93%) and only a very minor fraction to sludge (5%)*", i.e. "*indirect exposure for this material is considered very low*", and that the Substance is not very toxic to aquatic organisms.

Effects on terrestrial organisms are an information requirements under Annex IX to REACH (Section 9.4.).

In respect of the argument that the requirements for the information on effects on terrestrial organisms is triggered by the outcome of risk assessment, Annex IX, Section 9.4., Column 2 does not allow omitting the need to submit this information as required under Column 1.

However, as explained in ECHA Guidance R.7c (section R.7.11.6.3), there is an option of screening hazard and risk assessment, based on soil hazard categories. There is no information on the half-life of the Substance in soil (e.g. as explained in ECHA Guidance R.7b and R.11, degradation simulation studies performed in appropriate environmental media and at environmentally realistic conditions are the tests that can provide a definitive degradation half-life in the relevant compartment). As further noted in the Guidance R.11, in general, results of a single simulation degradation study cannot be directly extrapolated to other environmental compartments, i.e. in general, half-life in one compartment cannot be directly extrapolated to half-life in other environmental compartments. Therefore, as explained above, the Substance is considered to be very persistent in soil compartment (which is default setting for non-readily biodegradable substance if no information on half-life in soil is available). Thus, the Substance would fall into soil hazard category 3 or 4.

Furthermore, for the reasons explained under requests in the Appendix A, Sections 1, 2 and 3, your dossier does not include reliable hazard information for the Substance on pre-natal developmental toxicity and long-term aquatic toxicity. Thus, a newly generated information might indicate the need to classify the Substance to a specific hazard classes or categories and trigger the need for the exposure assessment and risk characterisation as well as to indicate that the Substance is very toxic to aquatic organisms (e.g. the Substance would meet the classification criteria for classification aquatic category chronic 1). Therefore, accurate allocation of an appropriate soil hazard category either 3 or 4 according to table R.7.11-2 (ECHA Guidance R.7c) is not possible at this time for the Substance. Consequently, it is not possible to omit the standard information requirements for the terrestrial compartment through an initial screening assessment based upon the EPM, mentioned in Annex IX, Section 9.4, Column 2. If after the information on long-term aquatic toxicity is gathered the Substance falls into soil hazard category 3, a confirmatory long-term soil toxicity test (on invertebrates or plants) might be sufficient if there is no indication of risk for soil compartment. If you conclude that no further investigation of effects on terrestrial organisms is required for any of standard information requirements (e.g. after performing one of confirmatory long-term toxicity tests on soil invertebrates or plants and toxicity test with soil micro-organisms), you should update your technical dossier by clearly stating the reasons for adapting the remaining information requirement(s) of Annex IX, Section 9.4. of the REACH Regulation.

Finally, there is no exposure assessment reported in the chemical safety report provided in the registration dossier which would support your notion that the exposure of soil compartment by the Substance is unlikely. In the registration dossier there are professional and consumer uses which indicate the contrary. E.g. for identified use by consumers in washing and cleaning products with assigned ERC 8d default release factor to soil would be 20% (ECHA Guidance R.16). Furthermore, results of your provided modelling of the fate of the Substance in waste water treatment plant indicates that the indirect exposure of the soil compartment by the Substance via application of the sludge from waste water treatment plant is not unlikely, as the fraction partitioning to sludge is 5%.

On this basis, the information requirement is not fulfilled.

Study design

The earthworm reproduction test (OECD TG 222), Enchytraeid reproduction test (OECD TG 220), and Collembolan reproduction test (OECD TG 232) are each considered capable of generating information appropriate for the fulfilment of the information requirement for long-term toxicity testing on terrestrial invertebrates.

ECHA is not in a position to determine the most appropriate test protocol, since such determination is dependent upon species sensitivity and substance properties.

5. Effects on soil micro-organisms

Effects on soil micro-organisms is an information requirement under Annex IX to REACH (Section 9.4.2.).

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a toxicity study with soil micro-organisms (OECD TG 216) with an analogue substance.

As explained in the Appendix on reasons common to several requests your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

In your comments on the initial draft decision, you provide the same comments as for the Long-term toxicity testing on terrestrial invertebrates which are addressed in the Appendix A, section 4 above. In addition, ECHA emphasises that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method and therefore the potential adaptation possibility outlined for the information requirement of Annex IX, Section 9.4. does not apply for the endpoint of Effects on soil micro-organisms.

6. Long-term toxicity on terrestial plants

Short-term toxicity to plants is an information requirement under Annex IX to REACH (Section 9.4.3.). Long-term toxicity testing on plants must be considered (Section 9.4., Column 2) if the substance has a high potential to adsorb to soil or is very persistent.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. In support of your adaptation you provided a long-term toxicity study on plants (OECD TG 208 with six species) with an analogue substance.

Based on the information provided in the registration dossier, the Substance is not readily biodegradable (10% degradation after 28 days in key study according to OECD TG 301F) and there is no half-life of the Substance in soil available, therefore the Substance is considered to be very persistent (ECHA Guidance R.7c). Thus, the long-term toxicity testing on terrestrial organisms is required.

As explained in the Appendix on reasons common to several requests your adaptation is rejected.

In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

Estimation of effect concentration

To fulfil the information requirement, a study must comply with the OECD TG 208 (with at least six species) or ISO 22030. Therefore, the following requirements must be met:

Key parameter to be measured:

- the concentrations of the test material leading to no observed effect concentration (NOECs) on the following parameters are estimated:
  a) in OECD TG 208:
     1) plants emergence and visual phytotoxicity and mortality;
     2) biomass of surviving plants;

3) shoot height of the plants.

b) In ISO 22030:
   1) inhibition of the growth;
   2) reproductive capability of higher plants.

As explained in ECHA Guidances R.7c, Section R.7.11.5.3 (p.153) and R.10, Sections R.10.6.3 (p. 41) and R.10.3.1.3 (p. 21-22) 'averaging' of data to a single value of (no-)effect concentration could be applied when multiple data for one species and same endpoint are available.

In the registration dossier as the key parameter value you reported effect concentration (EC10) estimated as average results from six different plant species.

As explained above, averaging of effect concentrations from various species should not be done and the lowest NOEC from the single species in the study should be reported and used as key parameter value. Thus, your estimation of key parameter, i.e. NOEC, is not acceptable.

In your comments on the initial draft decision, you provide the same comments as for the Long-term toxicity testing on terrestrial invertebrates which are addressed in the Appendix A, section 4 above.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. Testing shall be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD TG 208 guideline. You should consider if testing on additional species is required to cover the information requirement.

Terrestrial plants, growth test (OECD TG 208 with at least six species) and Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030) are each considered capable of generating information appropriate for the fulfilment of the information requirement for long-term toxicity testing on terrestrial plants.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[9].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)
   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[10].

[9] https://echa.europa.eu/practical-guides
[10] https://echa.europa.eu/manuals

Appendix C: General recommendations when conducting and reporting new tests for REACH purposes

A. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (Section R.11.4.2.2), you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthetize its relevant constituents and/or fractions.

Appendix D: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 22 May 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 request(s).

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

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

Appendix E: List of references - ECHA Guidance[11] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

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

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

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

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

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

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

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

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

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

OECD Guidance documents[13]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

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

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

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

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

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

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

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