~~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
27/05/2020

Registered substance subject to this decision ("the Substance")
Substance name: Cyclacet
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 in A.1, B.3, B.4, and C.1 below by ***27 July 2022*** and all other information listed below by ***27 July 2023***.

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

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

1. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105/OECD GD 29)

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

3. Only if study under section A1 shows the substance is not poorly water soluble, Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

4. Only if study under section A1 show the substance is poorly water soluble, Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

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

6. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301A/B/C/D/E/F or OECD TG 310)

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

1. 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)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

4. Only if study under section A1 shows the substance is not poorly water soluble, Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

5. Only if study under section A1 shows the substance is poorly water soluble, Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

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

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

2. 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)

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

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

5. Short-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1.; test method: EU C.8./OECD TG 207) or 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)

6. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216)

7. Short-term toxicity on terrestrial plants (Annex IX, Section 9.4.3; test method: OECD TG 208, with at least three species) or 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";
- Appendices entitled "Reasons to request information required under Annexes VII to 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.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

Appendix 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:

- Water solubility (Annex VII, Section 7.7)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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

Grouping of substances and read-across approach

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Predictions for toxicological and environmental fate properties

You have not provided any read-across justification document in the technical dossier.

You read-across between the structurally similar substances,

1. CAS 5413-60-5, 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden-6-yl acetate, EC 226-501-6
2. CAS 3407-42-9, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, EC 222-294-1
3. CAS 77-73-6, Dicyclopentadiene, 3a,4,7,7a-tetrahydro1H-4,7-methano-indene, EC 201-052-9
4. CAS 66068-84-6, 3-(2,3,3-trimethyl-6-bicyclo[2.2.1]heptanyl)cyclohexan-1-ol, EC 266-100-3
5. CAS 32210-23-4, 4-tert-butylcyclohex yl acetate, EC 250-954-9
6. CAS 5413-60-5, Jasmacyclen, EC 226-501-6

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

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

7. CAS 79-20-9, methyl acetate, EC 201-185-2
8. CAS 141-78-6, ethyl acetate, EC 205-500-4

as source substance and the Substance as target substance.

You have not provided a reasoning for the prediction of toxicological properties.

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.

ECHA notes the following shortcomings with regards to predictions of toxicological and environmental fate properties.

1. *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]

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).

2. *Supporting information - Missing supporting information to compare properties of the substances*

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*"[5]. 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 bridging studies to compare properties of the Substance and source substances.

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).

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1
[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

Your dossier does not contain studies that were conducted with the Substance; only studies with source substances. Two studies (OECD TG 407, OECD TG 471) were conducted with a substance that corresponds to a constituent of your substance. However, more than 50% of the typical composition are unaccounted for. Therefore the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and of the source substances to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and of the source substance(s) 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.

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2

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

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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

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

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

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

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

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

1) Relevance of the different pieces of information

The sources of information need to provide sufficient weight of evidence to conclude that the information requirements for OECD TG 471, OECD TG 473/487, OECD TG 476/490 and OECD TG 414 are fulfilled for the properties *in vitro* gene mutation in bacteria and mammalian cells, *in vitro* chromosomal aberration in mammalian cells, and prenatal developmental toxicity.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirements proposed to be adapted and identified deficiencies in the endpoint sections A.2, B.1, B.2 and C.2.

2) Reliability of the read across approach

Information from source substance(s) can be used as part of weight of evidence adaptation if the read-across is accepted.

All studies are performed with analogue substances. For the reasons explained under Section 1. of the Appendix on Reasons common to several requests, the information on the analogue substances does not provide reliable information for weight-of-evidence. Therefore they do not contribute to the weight-of-evidence adaptation.

Additional issues related to reliability of the sources of information for the weight of evidence are addressed under the corresponding endpoints in Appendices A-C.

3. Assessment of your adaptation for effects on terrestrial organisms

You have provided the same Annex IX, Section 9.4., Column 2 adaptation for the following standard information requirements:

- Short-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1.)
- Effects on soil micro-organisms (Annex IX, Section 9.4.2)
- Short-term toxicity to terrestrial plants (Annex IX, Section 9.4.3.)

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.4., Column 2. In support of your adaptation you provided the following justification: *"In accordance with column 2 of Annex IX of the REACH regulation, the study does not need to be conducted because direct and indirect exposure of the soil compartment is less as considering its use in fragrances."* Furthermore, in the chemicals safety report (CSR) you provided exposure assessment and risk characterisation for soil compartment which is based on the predicted no-effect concentration PNEC for soil organisms derived from the PNEC for aquatic organisms using equilibrium partitioning method (EPM).

In the registration dossier you provide for the Substance half-life value of 30 days in soil predicted by the application of Level III Fugacity Model (EPI Suite version 4.1).

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

Rejection of adaptation based on exposure considerations
According to Annex IX, Section 9.4., Column 2 soil toxicity testing may be omitted if direct and indirect exposure of the soil compartment is unlikely.

In the CSR you report a number of various industrial uses of the substance where direct and indirect exposure of the soil is identified in the respective exposure scenarios (ESs) by the release factor to the soil and/or estimated predicted environmental concentration (PEC) in soil being not equal to zero. Thus, your adaptation based on exposure considerations is not supported by the exposure assessment reported in the CSR. Therefore, the soil exposure is not unlikely and your adaptation is rejected.

Rejection of the screening assessment
In the absence of toxicity data for soil organisms, the EPM may be applied to assess the hazard to soil organisms. According to ECHA Guidance R.7c, Section R.7.11.6, where there is adequate data available to derive a PNEC for aquatic organisms, this PNEC can be used in a screening assessment of risks for soil through the use of the EPM approach. Furthermore, for the screening assessment, i.e. allocation to the relevant soil hazard category, and for the triggering of long-term toxicity testing on the basis of Column 2, Section 9.4 of Annex IX, according to section R.7.11.6.3. of ECHA Guidance R.7c, substances that are ionisable or have a log K_{ow}/K_{oc} >5 are considered highly adsorptive, whereas substances with a degradation half-life >180 days are considered very persistent in soil (default setting, unless classified as readily biodegradable).

For the reasons explained under requests in the A. 3-5., B.4-5. and C.3-4., your dossier does not include reliable hazard information for the Substance on aquatic organisms from at least three trophic levels. Therefore, a reliable PNEC for aquatic organisms cannot be derived, and consequently, PNEC for soil organisms through the use of EPM approach cannot be derived and screening assessment for soil compartment cannot be performed (ECHA Guidance R.7c, Section R.7.11.6).

Moreover, for the reasons explained under requests in the A.6. your dossier does not include reliable information on the ready biodegradability of the Substance. Furthermore, for the prediction of degradation half-life in soil you used the fugacity model which is based on predicted ready biodegradability information, i.e. is not appropriate to derive degradation half-life value in soil under environmentally relevant conditions and which estimates the half-life representing not only degradation, but also advection, i.e. removal of chemical from a compartment through losses other than degradation (reaction), processes (ECHA Guidance R.7b and R.11). Therefore, your dossier currently does not include reliable information to establish if the substance is very persistent.

Thus, accurate allocation of an appropriate soil hazard category according to table R.7.11-2 (ECHA Guidance R.7c) is not possible at this time. Consequently, it is not possible to omit the standard information requirements for the toxicity to soil organisms through an initial screening assessment based upon the EPM, mentioned in Annex IX, Section 9.4, Column 2.

Thus, your adaptation is rejected.

Triggering of the long-term soil toxicity testing

Annex IX, section 9.4., column 2, requires to perform a long-term toxicity studies on terrestrial invertebrates and plants instead of a short-term tests when the substance has a high potential to adsorb to soil or is very persistent.

As explained above, your dossier currently does not include reliable information to establish if the substance is persistent. Therefore, if the data generated under requests A.6. confirms that the Substance is persistent then long-term toxicity testing on soil invertebrates and plants must be conducted.

4. Assessment of your adaptations for the aquatic toxicity testing

Short-term toxicity testing on aquatic invertebrates , growth inhibition study aquatic plants and short-term toxicity testing on fish are information requirements under Annex VII, Sections 9.1.1. and 9.1.2. and of Annex VIII, Section 9.1.3. respectively. Long-term toxicity testing on aquatic invertebrates and on fish are an information requirements under Annex IX, Sections 9.1.5. and 9.1.6. respectively.

For all these information requirements you provide an adaptation in which you refer to Annex VIII, column 2 and note that the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

We have assessed this information and identified the following issues:

Rejection of adaptation for information requirements under Annex VII, Sections 9.1.1. and 9.1.2. and Annex VIII, Section 9.1.3.

Under Column 2 of Annex VII, Sections 9.1.1. and 9.1.2. and of Annex VIII, Section 9.1.3., the respective study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. ECHA Guidance R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of a high bioaccumulation potential (ECHA Guidance R.11, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* D_{max} > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (log K_{ow} > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

Unless it can reliably be demonstrated that aquatic toxicity is unlikely to occur, the Substance must be considered as poorly water soluble.

As explained under request A.1, your dossier currently does not include reliable data on the water solubility of the substance. More specifically, the studies discussed under request A.1 are not compliant and do not allow the determination of a precise value for water solubility.

Furthermore, there is a number of mammalian and ecotoxicity studies requested in this decision, you reported: log Kow value of 4.2 for the Substance (section 4.7 of the registration dossier); molecular weight of the main constituents of [redacted] (section 1.2 of the registration dossier); and no information on other indicators of hindered uptake.

Therefore, you have not demonstrated the low likelihood of the substance to cross biological membranes.

Therefore, you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected.

Triggering of the long-term aquatic toxicity testing

Column 2 of Annex VII, Section 9.1.1. and of Annex VIII, Section 9.1.3., requires to perform a long-term toxicity study instead of a short-term test when the substance concerned is poorly water soluble. In that respect, as explained under request A.1, your dossier currently does not include reliable value on the water solubility of the substance. Therefore, a short-term toxicity testing on aquatic invertebrates and fish must only be conducted if the data generated under request A.1 do not confirm that the substance is poorly water soluble (e.g. water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5)).

If the data generated under request A.1 confirm that the substance is poorly water soluble, then the long-term toxicity testing with aquatic invertebrates and fish is required, because poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances.

Rejection of adaptation for information requirements under Annex IX, Sections 9.1.5. and 9.1.6.

A registrant may only adapt information requirements under Annex IX, Sections 9.1.5. and 9.1.6. based on the general rules set out in Annex XI.

Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

Therefore you have not justified that this information can be omitted..

On this basis, the information requirements under Annex VII, Sections 9.1.1. and 9.1.2., Annex VIII, Section 9.1.3., and Annex IX, Sections 9.1.5. and 9.1.6. are not fulfilled.

5. Data sharing issues

The jointly submitted registration for the Substance contains data which is relevant for the following requests: A.1, A.3, A.5, A.6. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[6].

The jointly submitted registration for the Substance contains data which is relevant for the request under B.3, B.4, C.1. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[6]

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report.

[6] https://echa.europa.eu/regulations/reach/registration/data-sharing

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

1. Water solubility

Water solubility is a standard information requirement in Annex VII to REACH.

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

- A key study using the flask method (2014) with source substance CAS 5413-60-5
- A supporting study 2018 supporting study from a handbook with source substance CAS 5413-60-5

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

A. Read-across

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

B. Key study

EU test method A.6 and OECD TG 105 describe two methods (the column elution method and the flask method) for conducting the study. The test method must be selected based on a water solubility estimate obtained in a preliminary study. For substances with preliminary water solubility below 10 mg/L the column elution method must be used.

You have provided a study performed with the flask method and you report a water solubility 0.01 mg/L. The reported result falls outside of the applicability domain of the flask method.

Therefore, the provided information does not fulfil the information requirement.

Study design

Considering the properties of the Substance (solubility < 10 mg/L), the column elution described in EU A.6/OECD TG 105 is the most appropriate method to fulfil the information requirement for the Substance.

2. In vitro gene mutation study in bacteria

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

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

i. 1980 *in vitro* gene mutation in bacteria (OECD TG 471, secondary literature) with source substance CAS 5413-60-5
ii. 2018 in vitro gene mutation in bacteria (OECD TG 471) with source substance CAS 3407-42-9

iii. 1987 *in vitro* gene mutation in bacteria (OECD TG 471) with source substance CAS 77-73-6

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

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

To fulfil the information requirement, normally a study according to OECD TG 471 must be provided. The key elements investigated by this test are:

- 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 provided on 5 bacterial 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).

The provided studies detect and quantify mutations in bacteria. However, the provided studies (i. and iii.) do not include data on the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). Therefore, the provided studies only provide partly relevant information.

Furthermore, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information are for this information requirement affected by the following issues. Testing in accordance with OECD TG 471 requires that the following specifications/ conditions have to be met:

a) The test must be performed with 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)
b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
e) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

The reported data for the studies you have provided did not include:

a) results for the appropriate 5 strains, that is in TA98/TA100/TA1535/TA1537 or TA97a or TA97/the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) (studies i., iii.),
b) a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance (studies ii., **Error! Reference source not found.**.),
c) a positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control (study i.),
d) a negative control with a number of revertant colonies per plate inside the historical

control range of the laboratory (study i.),

e) data on the number of revertant colonies per plate for the treated doses and the controls (studies i., iii.).

Therefore, the provided studies cannot be considered reliable sources of information.

As a conclusion, the sources of information provide information on mutations in bacteria which is only partly relevant, and the information provided is not reliable.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated by the required study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

3. Short-term toxicity testing on aquatic invertebrates

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

You have provided an adaptation under Annex VII, Section 9.1.1, Column 2 with the following justification: the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

We have assessed this information and identified the following issues:

As explained in Appendix on Reasons common to several requests, Section 5 your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

As explained in Appendix on Reasons common to several requests, Section 5 a short-term toxicity testing on aquatic invertebrates must only be conducted if the data generated under request A.1 do not confirm that the substance is poorly water soluble.

Study design

The Substance is difficult to test due to the adsorptive properties (log Kow equal to 4.2) and might be poorly water soluble. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

4. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII of REACH. Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

- You have provided an adaptation under Annex VII, Section 9.1.1, Column 2 with the following justification: the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

As explained in Appendix on Reasons common to several requests, Section 5 if the data generated under request A.1 confirm that the substance is poorly water soluble, then the long-term toxicity testing with aquatic invertebrates is required.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Appendix C.3.

5. Growth inhibition study aquatic plants

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

You have provided an adaptation under Annex VII, Section 9.1.2, Column 2 with the following justification: the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

We have assessed this information and identified the following issue:

As explained in Appendix on Reasons common to several requests, Section 5 your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

6. Ready biodegradability

Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

You have adapted this information requirement by using Weight of Evidence under Annex XI, Section 1.2.

You have provided the following information to support your adaptations:

- QSAR calculation (2018). EPI/BioWin v.4.10 with source substance CAS 5413-60-5
- Experimental study (2018). Data from authoritative database with source substance CAS 79-20-9 / EC 201-185-2
- Experimental study (2018). Data from authoritative database with source substance 141-78-6 / 205-500-4

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

Weight of evidence

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

To fulfil the information requirement, normally a study according to OECD TG 301A/B/C/D/E/F or 310 must be provided. The key parameter investigated by this test is the ultimate aerobic biodegradation (as measured by parameters such as DOC removal, CO2 production and oxygen uptake) of the test material under low inoculum concentration measured at sufficiently frequent intervals to allow the identification of the beginning and end of biodegradation.

All the sources of information you provided investigate this key parameter. Therefore, they provide information that would contribute to the conclusion on this key parameter.

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

In addition, ECHA has identified additional deficiencies presented below.

Reliability of the QSAR estimation

Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:
1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

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

The prediction is not adequate due to low reliability

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with information available for other related endpoint(s).

The predictions for the source substance used as input are not reliable because there are no similar substances in the training sets of the models. Furthermore, the bulky structure of the substance and possible steric hindrance may affect biodegradation, which the models do not account for.

Therefore, you have not demonstrated that the prediction is reliable, so the results are not adequate for the purpose of risk assessment or classification and labelling.

Reliability of experimental studies provided

To fulfil the information requirements of Annex VII, Sections 9.2.1.1. a study must comply with OECD TG 301 or 310 (Article 13(3) of REACH). Therefore, the following specifications must be met:

- The source of the inoculum and any pre-conditioning treatment are reported;
- The test temperature is reported;
- The methods of preparation of test solutions/suspensions is reported;
- The results of measurements at each sampling point in each replicate is reported in a tabular form;
- Any observed inhibition phenomena and/or abiotic degradation are reported.

Your registration dossier provides two experimental studies without information reported, as specified above. Therefore, the reporting of the studies is not sufficient to conduct an independent assessment of their reliability.

Taken together, even if these sources of information provide information on the key parameters, their reliability is affected so significantly that they cannot be taken into consideration in a weight of evidence approach.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated by in an OECD TG 301 or 310 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

On this basis, the information requirement is not fulfilled.

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

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

i. *year unknown* (database check 2018) *in vitro* mammalian chromosome aberration test (OECD TG 473) with source substance CAS 77-73-6,
ii. 2018 *in vitro* mammalian chromosome aberration test (OECD TG 473) with source substance CAS 3407-42-9.

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

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

To fulfil the information requirement, normally a study according to OECD TG 473 or OECD TG 487must be provided. The key elements investigated by this test are:

- Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

The provided studies detect and quantify structural or numerical chromosomal aberrations in cultured mammalian cells. Therefore, they provide relevant information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information are for this information requirement affected by the following issues. Testing in accordance with OECD TG 473 or OECD TG 487 requires that the following specifications/ conditions have to be met:

a) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

The reported data for the study i. you have provided did not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance
b) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

Therefore, the provided studies cannot be considered reliable sources of information.

As a conclusion, the sources of information provide information on structural or numerical chromosomal aberrations in cultured mammalian cells which is relevant, but the information provided is not reliable.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated by the required study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, either *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) are considered suitable.

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

Your dossier contains an adaptation for an *in vitro* gene mutation study in bacteria, and an adaptation for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in sections A.2 and B.1 of the Appendices A and B.

The result of the requests for information in sections A.2 and B.1 of these Appendices will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ii. Assessment of information provided

You have adapted this information requirement by using Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

i. 2015 in vitro mammalian cell gene mutation test (OECD TG 476) with source substance CAS 3407-42-9,
ii. 2015 in vitro mammalian cell gene mutation test (OECD TG 476) with source substance CAS 66068-84-6.

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

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

To fulfil the information requirement, normally a study according to OECD TG 476 or OECD

TG 490 must be provided. The key elements investigated by these tests are:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (in vitro).

The provided studies detect and quantify mutations in mammalian cells. Therefore, they provide relevant information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information are for this information requirement affected by the following issues. Testing in accordance with OECD TG 476 or OECD TG 490[7] requires that the following specifications/ conditions have to be met:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.

The reported data for the study ii. you have provided do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.

Therefore, the provided studies cannot be considered reliable sources of information.

As a conclusion, the sources of information provide information on mutations in mammalian cells which is relevant, but the information provided is not reliable.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated by the required study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

Study design

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

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

You have adapted this information requirement by using a *grouping and read-across* approach under Annex XI, Section 1.5 using the following source studies:

i. 2015 sub-acute (28d) RDT study (OECD TG 407) with the source substance CAS 5413-60-5,
ii. 2011 combined repeat dose and reproductive / developmental toxicity screening test (OECD TG 422) with the source substance CAS 77-73-6,
iii. 2007 pre-natal developmental toxicity study (~OECD TG 414) with the source substance CAS 32210-23-4,
iv. 2018 screening for reproductive / developmental toxicity screening test (OECD TG 421) with the source substance CAS 17511-60-3, 43 days,

As explained in the Appendix on general considerations your adaptation is rejected. In addition, the following endpoint-specific deficiencies have been identified in your adaptation:

To be considered compliant and to generate information concerning the effects of the Substance on male and female reproductive performance, the study has to meet the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422. The criteria of this test guideline include for example:

a. At least 10 male and 12-13 female animals for each test and control group,
b. Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation,
c. Examination of key parameters for hormone assessment (P0 and F1) such as thyroid parameters, hormone levels, anogenital distance/number of nipples/areolae in male pups,
d. Examination of parameters for sexual function and fertility such as /those for mating and fertility/duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues,
e. Monitoring of oestrus cycles,
f. Examination of offspring parameters such as /number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/number of nipples/areolae in male pups,

The reported data for the studies you have provided do not include:

a. At least 10 male and 12-13 female animals for each test and control group (studies i., iii.),
b. Dosing for a minimum of 28 (males) and ~63 days (females) (studies i., iii., iv.)
c. Examination of key parameters for hormone assessment (P0 and F1) (studies i., ii., iii., iv.)
d. Examination of parameters for sexual function and fertility (studies i., iii., iv.),
e. Monitoring of oestrus cycles (studies i., iii., iv.)
f. Examination of offspring parameters (study i.).

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

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[8] administration of the Substance.

2. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH

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

(Section 9.1.3).

You have provided an adaptation under Annex VIII, Section 9.1.3., Column 2 with the following justification: the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

We have assessed this information and identified the following issues:

As explained in Appendix on Reasons common to several requests, Section 5 your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

As explained in Appendix on Reasons common to several requests, Section 5 a short-term toxicity testing on fish must only be conducted if the data generated under request A.1 do not confirm that the substance is poorly water soluble.

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

3. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble

- You have provided an adaptation under Annex VIII, Section 9.1.3., Column 2 with the following justification: the Substance is highly insoluble in water, hence aquatic toxicity is unlikely to occur.

As explained in Appendix on Reasons common to several requests, Section 5 if the data generated under request A.1 confirm that the substance is poorly water soluble, then the long-term toxicity testing with aquatic invertebrates is required.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Appendix C.4.

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

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

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

You have adapted this information requirement by using a *grouping and read-across* approach under Annex XI, Section 1.5 using the following source study:

i. 2015 sub-acute (28d) RDT study (OECD TG 407) with the source substance CAS 5413-60-5.

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

A. Read-across

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected. In addition, we have identified the following deficiency:

B. Study quality

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:

1. At least 10 female and 10 male animals should be used at each dose level (including control group),
2. Dosing of the Substance daily for a period of 90 days until the scheduled termination of the study,
3. Clinical observations, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, recording of body weight, hematology, clinical biochemistry including hormone measurements, and pathology of sexual (male and female) organs, full detailed gross necropsy and subsequent histopathology as specified by OECD TG 408.

The repeated dose oral toxicity study (OECD TG 407) you provided does not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 days, and it was conducted with less than 10 animals per sex per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408. You did not report, as specified by OECD TG 408, the organ weights of adrenals, prostate & seminal vesicles with coagulating glands; the histopathology of spinal cord, eye, thyroid, trachea, epididymides, prostate and seminal vesicles with coagulating glands), vagina, urinary bladder, skeletal muscle and bone; nor investigations such as thyroid weight, THS/T3/T4 levels, and estrous cycling

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

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation.

2. 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 Grouping of substances and read-across approaches under Annex XI, Section 1.5., and Weight of Evidence under Annex XI, Section 1.2. of REACH.

You have provided the following sources of information to support your adaptations:

i. 2011 combined repeat dose and reproductive / developmental toxicity screening test (OECD TG 422) with the source substance CAS 77-73-6,
ii. 2007 pre-natal developmental toxicity study (~OECD TG 414) with the source substance CAS 32210-23-4,
iii. 1973/RL4, secondary source, teratologic evaluation of test chemical in rabbits

We agree that study iii. is unassignable/unreliable.

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

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

To fulfil the information requirement, normally a study according to OECD TG 414 must be provided. The key elements investigated by these tests are:

- 1) prenatal developmental toxicity including structural gross, visceral and skeletal malformations and variations, 2) maternal toxicity, and 3) maintenance of pregnancy.

The provided study i. provides information only on 2) maternal toxicity, and 3) maintenance of pregnancy. Study ii. additionally provides information on 1) prenatal developmental toxicity including structural gross, visceral and skeletal malformations and variations.

Therefore, the provided studies only provide partly relevant information.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 1 of the Appendix on Reasons common to several requests.

Therefore, the provided studies cannot be considered reliable sources of information.

As a conclusion, the sources of information provide information on pre-natal developmental toxicity which is only partly relevant, and the information provided is not reliable.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated by the required study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Information on the study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[9] administration of the Substance.

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

3. 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.).

Generic description

You have provided the following a justification to omit the study: *"in accordance with column 2 of Annex VIII of the REACH regulation, testing for this end point is considered scientifically unjustified since there are mitigating factors indicating that aquatic toxicity is unlikely to occur as the substance is highly insoluble in water. Thus substance can be considered to be hydrophobic in nature."*

We have assessed this information and identified the following issue:

As explained in Appendix on Reasons common to several requests, Section 5 your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

4. Long-term toxicity testing on fish

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

You have provided the following justification to omit the study *"in accordance with column 2 of Annex VIII of the REACH regulation, testing for this end point is considered scientifically unjustified since there are mitigating factors indicating that aquatic toxicity is unlikely to occur as the substance is highly insoluble in water. Thus substance can be considered to be hydrophobic in nature."*

We have assessed this information and identified the following issue[s]:

As explained in Appendix on Reasons common to several requests, Section 5 your adaptation is rejected.

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.). OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.3.

5. Short-term toxicity to terrestrial invertebrates or Long-term toxicity on terrestrial 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 provided an adaptation under Annex IX, Section 9.4., Column 2 with the following justification: *"In accordance with column 2 of Annex IX of the REACH regulation, the study does not need to be conducted because direct and indirect exposure of the soil compartment is less as considering its use in fragrances."*

We have assessed this information and identified the following issue[s]:

Rejection of adaptation
As explained in Appendix on Reasons common to several requests, Section 4 your adaptation is rejected.

Triggering of the long-term soil toxicity testing
As explained in Appendix on Reasons common to several requests, Section 4, if the data generated under requests A.6. confirms that the Substance is persistent then long-term toxicity testing on soil invertebrates must be conducted.

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.

6. 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 provided an adaptation under Annex IX, Section 9.4., Column 2 with the following justification: "*In accordance with column 2 of Annex IX of the REACH regulation, the study does not need to be conducted because direct and indirect exposure of the soil compartment is less as considering its use in fragrances*."

We have assessed this information and identified the following issue:

As explained in the Appendix on reasons common to several requests, Section 4 your adaptation is rejected.

Furthermore, 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 present endpoint.

On this basis, the information requirement is not fulfilled.

7. Short-term toxicity on terrestrial plants or Long-term toxicity on terrestrial 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 provided an adaptation under Annex IX, Section 9.4., Column 2 with the following justification: *"In accordance with column 2 of Annex IX of the REACH regulation, the study does not need to be conducted because direct and indirect exposure of the soil compartment is less as considering its use in fragrances."*

We have assessed this information and identified the following issues:

Rejection of adaptation
As explained in Appendix on Reasons common to several requests, Section 4 your adaptation is rejected.

Triggering of the long-term soil toxicity testing
As explained in Appendix on Reasons common to several requests, Section 4, if the data generated under requests A.6. and confirms that the Substance is persistent then long-term toxicity testing on soil plants must be conducted.

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 short-term toxicity testing, ECHA considers three species as the minimum to achieve a reasonably broad selection. Testing shall be conducted with species from different families, as a minimum with one monocotyledonous species and two 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.

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 D: 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[10].

B. Test material

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[11].

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

Appendix E: 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 24 June 2020.

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

ECHA did not receive any comments within the commenting period.

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 F: List of references - ECHA Guidance[12] 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)[13]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[14]

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[15]

[12] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[13] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[14] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[15] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

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

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

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

Appendix G: Addressees of this decision and their corresponding information requirements

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

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

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.