

Helsinki, 04 September 2023

Addressee(s)

Registrant(s) of JS_28645-51-4_█ as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision

07/10/2022

Registered substance subject to this decision ("the Substance")

Substance name: Oxacycloheptadec-10-en-2-one

EC/List number: 249-120-7

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 **10 December 2025**.

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

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

1. Skin sensitisation (Annex VII, Section 8.3)
 - a. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and
 - b. only if the *in vitro/in chemico* test methods specified under point a.) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);
2. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., Column 2; test method: EU C.20./OECD TG 211)
3. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201)

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

4. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei
5. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490)
6. Adsorption/desorption screening (Annex VIII, Section 9.3.1.; test method: EU C.18/OECD TG 106 or EU C.19/OECD TG 121)

7. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., Column 2; test method: EU C.47./OECD TG 210)

The reasons for the request(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

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.

Authorised¹ under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the request(s)

Appendix 2: Procedure

Appendix 3: Addressees of the decision and their individual information requirements

Appendix 4: Conducting and reporting new tests under REACH

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 1: Reasons for the request(s)

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Reasons common to several requests

0. Weight of evidence adaptation rejected

- 1 You have adapted the following standard information requirements by using Annex XI, Section 1.2. (weight of evidence). You have provided experimental data on the Substance, Oxacyclohexadecanone, CAS No. 34902-57-3, 3-methylcyclopentadecan-1-one, EC no 208-795-8, and Dodecane-12-lactam, EC no 213-424-8 for the following standard information requirements:
 - Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
 - 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.)
- 2 The test material used is different than the Substance for the in vitro studies . Therefore, the studies conducted with these substances (hereafter referred to as the "source substances") will be evaluated as a read-across adaptation as part of the weight of evidence assessment.
- 3 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.
- 4 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.
- 5 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 on the corresponding information requirement.

0.1. Lack of documentation justifying the weight of evidence adaptation

- 6 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.
- 7 You have not included a justification for your weight of evidence adaptation for each of the relevant information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.
- 8 In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation.

- 9 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.
- 10 The common deficiencies are set out here, while specific deficiencies are set out under the information requirement concerned in request 3 below.

0.1.1. Read-across adaptation rejected for toxicological standard information requirements

- 11 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 sections.
- 12 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.
- 13 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1.1. Absence of read-across documentation

- 14 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 include an explanation why the properties of the Substance may be predicted from information on the source substance(s).
- 15 You have provided robust study summaries for studies conducted with other substances than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance and thus why the properties of the Substance may be predicted from information on the source substance(s).
- 16 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substance(s).

0.1.1.2. Conclusion on the read-across approach

- 17 Based on the above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach is not reliable.

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

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

1.1. Information provided

19 You have provided:

- (i) a human patch test (2005) with the Substance;
- (ii) a human repeated insult patch test (2011) with the Substance;
- (iii) a open epicutaneous test (2011) with the source substance oxacycloheptadec-7-en-2-one, EC 231-929-1;
- (iv) a human maximization test (2011) with the source substance oxacycloheptadec-7-en-2-one, EC 231-929-1;
- (v) a human repeat insult patch test (2011) with the source substance oxacyclohexadecan-2-one, EC 203-354-6;
- (vi) a human maximization test (1975) with the source substance 1,4-dioxacycloheptadecane-5,17-dione, EC 203-347-8.

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Read-across adaptation rejected

20 For the same reasons as explained in Section 0.1.2, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected. In addition, ECHA identified endpoint specific issue(s) addressed in Sections 1.2.1.2 and 1.2.1.3.

1.2.1.2. Adequacy of the provided studies for hazard identification

21 A study on the Substance must be adequate for the corresponding information requirement. According to the Guidance on IRs and CSA, Section R.4 (page 1), "The evaluation of data quality includes assessment of adequacy of the information for hazard/risk assessment and C&L purposes". The Guidance on IRs and CSA, Section R.4 (page 1) defines adequacy as "the usefulness of data for hazard/risk assessment purposes". As a consequence, a study must be relevant for hazard assessment and for classification and labelling purposes.

22 This is also required in the case of read-across adaptation.

23 You have provided studies on humans according to the Human Maximization Test (HMT) (studies iv and vi), Human Repeat Insult Patch Test (HRIPT) (studies ii and v) and human patch test (study i), and you consider that the Substance is not a skin sensitiser.

24 The studies (i, ii, iv, v and vi) appear to have been designed to establish safe levels for specific intended uses for fragrances, rather than to investigate the intrinsic properties of the Substance as required for the purpose of hazard identification. In particular, the

dose levels used in these studies ranging between 0.5 to 30% and this is far lower that would be used for hazard identification purposes. In human maximization studies non-irritant liquids, as the Substance, are normally applied neat (100%) and here concentrations selected were 1% (study iv) and 30% (study vi). The objective of HRIPT is intended to confirm the absence of irritation and sensitisation potential and the method is not intended to be used for hazard identification purposes. The concentrations used in the HRIPTs confirm also this approach, as the concentrations were 0.5% (study ii) and 2% (study v). The human patch test (study i) has been designed to investigate whether a person has already been sensitised to a particular substance and not to investigate whether a substance has skin sensitising potential. Therefore, none of the studies allow to make a conclusion whether the Substance causes skin sensitisation.

25 Therefore, the studies are rejected and do not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.1.3. The provided study does not meet the specifications of the test guideline(s)

26 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case EU Method B.6/OECD TG 406. Therefore, the following specifications must be met:

- a) a dose level selection rationale is provided;
- b) information on exposure period/times of exposure is provided;
- c) the challenge dose is the highest non-irritation concentration;
- d) four different challenge concentrations should be used;
- e) positive and negative controls are included to establish the sensitivity and reliability of the experimental technique.

27 In study (iii):

- a) no dose level selection rationale was provided;
- b) no information on exposure period/times of exposure was provided;
- c) the concentration used for induction did not cause mild irritation;
- d) only one challenge concentration was reported; and the challenge concentration of 1% cannot be the highest non-irritating concentration, as the Substance is non-irritating to the skin;
- e) no information on positive and negative control group(s) were provided.

28 The information provided does not cover the specifications(s) required by OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

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

30 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1. above), this condition cannot be assessed.

31 On this basis, the information requirement is not fulfilled.

1.3. Specification of the study design

- 32 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.
- 33 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.
- 34 In your comment to the draft decision you explain that you will employ defined approaches (DAs) according to OECD TG 497 to determine the skin sensitisation potency of the Substance, and only if necessary perform an in vivo test. OECD TG 497 can be considered for fulfilling this information requirement; further ECHA guidance was provided (https://echa.europa.eu/documents/10162/1128894/oecd_test_guidelines_skin_sensitisation_en.pdf/40baa98d-fc4b-4bae-a26a-49f2b0d0cf63?t=1633687729588).
- 35 You remain responsible for complying with the REACH Regulation, including Annexes VII and XI, when applying OECD TG 497.

2. Long-term toxicity testing on aquatic invertebrates

- 36 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L

2.1. Triggering of the information requirement

- 37 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 and the long-term test is required.
- 38 In the provided experimental study (2015), the saturation concentration of the Substance in water was determined to be 0.015 mg/L.
- 39 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.
- 40 You have provided a short-term toxicity study on aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.
- 41 In the absence of information on long-term toxicity on aquatic invertebrates, this information requirement is not fulfilled.
- 42 Therefore, the information requirement is not fulfilled.

2.2. Comments on the draft decision

- 43 In your comments to the draft decision, you agree to perform the requested study.

2.3. Study design and test specifications

44 The Substance is difficult to test due to the low water solubility (0.015 mg/L). 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 201. 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.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

46 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on experimental data on the Substance, you have provided following information

(i) Growth inhibition study on aquatic plants/algae (2017) with the Substance;

47 You also have adapted this information requirement by using Column 2 of Annex VII, Section 9.1.2. To support the adaptation(s), you have provided following information:

(ii) A justification that there are mitigating factors indicating that aquatic toxicity is unlikely to occur as the Substance is highly insoluble in water.

3.2. Assessment of the information provided

48 As explained under Reasons common to several requests the weight of evidence adaptation already has critical deficiencies.

49 In addition, Annex XI, Section 1.2 states that there may be sufficient weight of evidence "from several independent sources of information".

50 You have only provided one source of information.

51 Therefore your adaptation is rejected.

52 In any case, as explained under Reasons common to several request, the adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

53 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.2. at Annex VII includes information covered by OECD TG 201.

54 Source of information (i) provides such information.

3.2.1. The provided study does not meet the specifications of the test guideline(s)

55 OECD TG 201 and the specifications of OECD GD 23 if the substance is difficult to test provide the following specifications:

Key parameter measured

- i) the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test are estimated. Growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period.

Validity criteria

- j) exponential growth in the control cultures is observed over the entire duration of the test;
- k) at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
- l) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is $\leq 35\%$.

Technical specifications impacting the sensitivity/reliability of the test

Characterisation of exposure

- m) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided.

56 In study (i):

Key parameter measured

- a) the concentrations of the test material leading to 0% (or 10%) inhibition of growth at the end of the test are not estimated.

Validity criteria

- b) -d) you claim that the validity criteria are fulfilled, however there are no raw data to verify the validity criteria.

Technical specifications impacting the sensitivity/reliability of the test

Characterisation of exposure

- e) no analytical monitoring of exposure was conducted.

57 Based on the above,

- the key parameter of OECD TG 201 is not completely covered
- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, information on analytical monitoring and analytical method is missing. Without analytical monitoring, it is not possible to determine whether and to what extent the tested organisms were exposed to the test material and thus the study is not reliable.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. More specifically, there are no raw data to check and confirm that the validity criteria are fulfilled.

58 On this basis, the specifications of OECD TG 201 are not met and there are significant reliability issues.

3.2.1.1. Conclusion

59 As a conclusion, the source of information as indicated above, provides information on the growth rate of algal cultures but the information provided is not reliable.

60 Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 201 study.

61 Based on the above, your adaptation is rejected.

3.2.2. The provided adaptation does not meet the criteria of Annex VII, Section 9.1.2., Column 2

62 Under Annex VII, Section 9.1.2., Column 2, first indent, the study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. Guidance on IRs and CSA, Section 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 (Guidance on IRs and CSA, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (e.g. $D_{\max} > 17.4 \text{ \AA}$ and $MW > 1100$ or $MML > 4.3 \text{ nm}$) or high octanol-water partition coefficient ($\log K_{ow} > 10$) or low potential for mass storage (octanol solubility (mg/L) $< 0.002 \times MW$), 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).

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

64 Your registration dossier provides:

- information on the solubility of the Substance in water (0.015 mg/L based on a non-guideline study);
- the following physico-chemical indicators: $MW = 252$ and octanol-water partition coefficient $\log K_{ow} = 6.7$.

65 Even though the water solubility of the Substance is low, the following does not support your justification:

- the physico-chemical indicators provided do not support a conclusion of hindered uptake .

66 Therefore, you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected and the Substance must be considered as poorly water soluble.

3.3. Comments on the draft decision

67 In your comments to the draft decision and in your updated dossier you provided new information, a growth inhibition study on aquatic plants/algae (2021) with the Substance.

- 68 We have assessed this information and identified the following issue:
- 69 Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.
- 70 Based on the information in your dossier, the study you provided is not performed in compliance with GLP.
- 71 Therefore, the information requirement is not fulfilled.

3.4. Study design and test specifications

- 72 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 and test specifications" under Request 2.

Reasons related to the information under Annex VIII of REACH**4. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study**

73 An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

4.1. Information provided

74 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on experimental data from the following substances:

- (i) an *in vitro* cytogenicity/chromosome aberration study in mammalian cells (2011) with the source substance Oxacyclohexadecenone, CAS No. 34902-57-3
- (ii) an *in vitro* cytogenicity/chromosome aberration study in mammalian cells (2011) with the source substance 3-methylcyclopentadecan-1-one, EC no 208-795-8.

4.2. Assessment of the information provided

75 As explained under Reasons common to several requests the weight of evidence adaptation already has critical deficiencies.

76 In addition, as explained under Reasons common to several request, the adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

77 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes:

- 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.

78 This information is covered by OECD TG 473 or OECD 487.

79 Both sources of information (i) and (ii) provide such information.

4.2.1.1. Reliability of the provided information

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

81 The information from (i) and (ii) with read across source substances is already rejected under Reasons common to several requests. Therefore they cannot be used as part of the weight of evidence adaptation.

4.2.1.2. Conclusion

82 In summary, the sources of information (i) and (ii) provide relevant information on cytogenicity. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for *in vitro* cytotoxicity study in mammalian cells.

83 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for *in vitro* cytotoxicity study in mammalian cells.

84 Based on the above, your adaptation is rejected.

85 Therefore, the information requirement is not fulfilled.

4.3. Comments on the draft decision

86 In your comments to the draft decision you agree to perform the requested study.

4.4. Specification of the study design

87 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the *in vitro* mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the *in vitro* mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations *in vitro*. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2). Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential *in vitro*. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

4.4.1. Assessment of aneugenicity potential

88 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

89 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

5. In vitro gene mutation study in mammalian cells

90 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, 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.

5.1. Triggering of the information requirement

91 Your dossier contains (I) a negative result for *in vitro* gene mutation study in bacteria, and (II) inadequate data for the other study (*in vitro* cytogenicity study in mammalian cells).

92 The *in vitro* cytogenicity study in mammalian cells provided in the dossier is rejected for the reasons provided in request 4.

93 The result of the request 4 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.

94 Consequently, you are required to provide information for this information requirement, if the *in vitro* micronucleus study provides a negative result.

5.2. Information provided

95 You have adapted this information requirement by using Annex XI, Section 1.2. (weight of evidence) based on experimental data from the following substances:

- (i) an *in vitro* gene mutation study in mammalian cells (2011) with the source substance Oxacyclohexadecanone, CAS No. 34902-57-3
- (ii) an *in vitro* gene mutation study in mammalian cells (2000) with the source substance Dodecane-12-lactam, EC no 213-424-8

5.3. Assessment of the information provided

96 As explained under Reasons common to several requests the weight of evidence adaptation already has critical deficiencies.

97 In addition, as explained under Reasons common to several request, the adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

98 Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.3 at Annex VIII includes similar information that is produced by the OECD TG 476/490 and OECD TG 488. This includes:

- 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) or mutant frequency for each tissue in mammals (in vivo).

99 Both sources of information (i) and ii) provide such information.

5.3.1.1. Reliability of the provided information

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

101 The information from (i) and (ii) with read across source substances is already rejected under Reasons common to several requests. Therefore they cannot be used as part of the weight of evidence adaptation.

5.3.1.2. Conclusion

102 In summary, the sources of information (i) and (ii) provide relevant information on *in vitro* gene mutation study in mammalian cells. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for *in vitro* gene mutation study in mammalian cells.

103 It is not possible to conclude, based on any source of information alone or considered together, on the information requirement for *in vitro* gene mutation study in mammalian cells.

104 Based on the above, your adaptation is rejected.

105 Therefore, the information requirement is not fulfilled.

5.4. Comments on the draft decision

106 In your comments to the draft decision you agree to perform the requested study.

5.5. Specification of the study design

107 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.

6. Adsorption/desorption screening

108 Adsorption/desorption screening is an information requirement under Annex VIII to REACH (Section 9.3.1).

6.1. Information provided

109 You have provided:

(i) an adsorption/desorption screening study (2017) with the Substance;

6.2. Assessment of the information provided

6.2.1. The provided study does not meet the specifications of the test guideline(s)

110 To fulfil the information requirement, a study must comply with the OECD TG 121 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Key parameter to be measured

- a) Coverage of the key parameter which is the adsorption coefficient K_{oc} as determined by the partition of the test material between the mobile solvent phase and the cyanopropyl stationary phase using reverse phase HPLC.

Technical specifications impacting the sensitivity/reliability of the test

- b) The solid phase consists of cyanopropyl chemically bound resins (e.g. Hypersil and Zorbax CN) chemically bound onto silica.

111 In study (i):

Key parameter to be measured

- a) The adsorption coefficient K_{oc} , as determined by the partition of the test material between the mobile solvent phase and the cyanopropyl stationary phase using reverse phase HPLC, was not determined.

Technical specifications impacting the sensitivity/reliability of the test

- b) the stationary phase of the HPLC column ('ZORBAX Eclipse Plus C18') chosen for the test is C18.

112 Based on the above,

- the key parameter of OECD TG 121 is not covered
- there are also critical methodological deficiencies resulting in the rejection of the study results. More, specifically, the use of a different stationary phase than the one contemplated in the OECD TG may have a significant impact on the results of the study.

113 On this basis, the specifications of OECD 121 are not met.

6.3. Comments on the draft decision

114 In your comments to the draft decision and in your updated dossier you provided new information, an adsorption/desorption study (2022) with the Substance. However, as with the study (i), you have not addressed the points i) and j) above.

115 Therefore, the information requirement is not fulfilled.

7. Long-term toxicity testing on fish

116 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

7.1. Triggering of the information requirement

117 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 and the long-term test is required.

118 As already explained in request 2, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

119 You have provided a short-term toxicity study on fish but no information on long-term toxicity on fish for the Substance.

120 In the absence of information on long-term toxicity on fish, this information requirement is not fulfilled.

121 Therefore, the information requirement is not fulfilled.

7.2. Comments on the draft decision

122 In your comments to the draft decision, you agree to perform the requested study.

7.3. Study design and test specifications

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

124 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 and test specifications" under Request 2.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

- Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

Guidance for monomers and polymers; ECHA (2012).

Guidance on intermediates; ECHA (2010).

All guidance documents are available online: <https://echa.europa.eu/guidance-documents/guidance-on-reach>

Read-across assessment framework (RAAF)

- RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:

<https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

OECD Guidance documents (OECD GDs)

- OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: 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 17 November 2021.

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

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

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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

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

Appendix 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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]
[REDACTED]	[REDACTED]	[REDACTED]
[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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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 summaries².
- (4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. 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.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

² <https://echa.europa.eu/practical-guides>

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (<https://echa.europa.eu/manuals>).