~~Confidential~~

Helsinki, 05 January 2023

Addressees
Registrant(s) of JS_Methylcyclopentane as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
02/03/2021

Registered substance subject to this decision ("the Substance")
Substance name: Methylcyclopentane
EC number: 202-503-2

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***14 April 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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: OECD TG 471, 2020)
2. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: EU C.4. A/B/C/D/E/F/OECD TG 301A/B/C/D/E/F or EU C.29./OECD TG 310)

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

3. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)
4. 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: EU B.17./OECD TG 476 or EU B.67./OECD TG 490)
5. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below
6. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by inhalation route, in rats
7. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: EU C.1./OECD TG 203)
8. Adsorption/ desorption screening (Annex VIII, Section 9.3.1.; test method: EU C.18/OECD TG 106 or EU C.19/OECD TG 121)

The reasons for the decision(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.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
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 decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

- 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.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Adsorption/desorption screening (Annex VIII, Section 9.3.1.)

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

3 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.

4 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. Predictions for (eco)toxicological and environmental fate properties

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

- 2-Methylpentane, EC No. 203-523-4.
- Hydrocarbons, C6, isoalkanes, <5% *n*-hexane, List No. 931-254-9.
- *n*-Hexane, EC No. 203-777-6.
- Hydrocarbons, C5 -C7, n-alkanes, isoalkanes, *n*-hexane rich, List No. 930-397-4.
- Hydrocarbons, C6, n-alkanes, isoalkanes, cyclics, *n*-hexane rich, List No. 925-292-5.

7 You provide the following reasoning for the prediction of (eco)toxicological and environmental fate properties: ”…these substances should be similar concerning physico-chemical properties, also their environmental fate, ecotoxicological and toxicological properties should be comparable”.

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issue(s) with the prediction(s) of (eco)toxicological and environmental fate properties:

0.1.1.1. Inadequate read-across hypothesis

10 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 other substances in the group, i.e. a read-across hypothesis.

11 This hypothesis should be based on recognition of the structural similarities and differences between the substances (Guidance on IRs and CSA, Section R.6.).It should also explain why the differences in the chemical structures should not influence the (eco)toxicological and environmental fate properties or should do so in a regular pattern, taking into account that variations in chemical structure can affect both toxicokinetics (uptake and bioavailability) and toxicodynamics (e.g. interactions with receptors and enzymes) of substances (Guidance on IRs and CSA, Section R.6.2.1.3).

12 Your read-across hypothesis is only based on structural similarities and similarities in the physico-chemical properties of the source substance(s) and the Substance. You consider that these elements are a sufficient basis for predicting the (eco)toxicological properties and the environmental fate properties of the Substance.

13 You have not substantiated how physico-chemical similarity alone would explain similarity in the predicted endpoint(s) and thus be sufficient to justify the toxicological/ ecotoxicological and environmental fate predictions.

14 Physico-chemical similarity alone does not necessarily lead to predictable or similar (eco)toxicological and environmental fate properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a (eco)toxicological or an environmental fate property, explaining why the structural differences do not influence toxicokinetics and toxicodynamics of the substances, and thus why the properties of the Substance may be predicted from information on the source substance(s).

0.1.1.2. Missing supporting information to compare properties

15 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 supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

16 Supporting information must include supporting information/bridging studies to compare properties of the Substance and source substances.

17 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 substances 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).

18 For the source substances, you provide the studies used in the prediction in the registration dossier. Apart from those studies, your read-across justification or the registration dossier does not include any robust study summaries or descriptions of data for the Substance that

would confirm that both the Substance and the source substances cause the same type of effects.

19 In the absence of such information, you have not established that the Substance and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

0.1.1.3. Read-across hypothesis contradicted by existing data

20 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 supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information must strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

21 The observation of differences in the toxicological properties between the source substance(s) and/or the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

22 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substances cause the same type of effect(s).

23 However, the results of the studies on repeated dose and specific target organ toxicity obtained with the source substances vary. Specifically, neurotoxicity is observed in several repeated dose toxicity studies conducted with the source substane n-hexane while negative results are reported in the neurotoxicity study with the source substance methyl-pentane. Methyl-pentane is a closer analogue of the Substance than n-hexane.

24 Accordingly, the source substance n-hexane has a harmonised classification as STOT RE 2 H373 based on its neurotoxic properties through inhalation, while the other source substances and the Substance are not classified for such effects.

25 The available set of data on the source substances indicates differences in the (eco)toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effects. However, you have not supported and scientifically justified why such differences in the (eco)toxicological properties do not affect your read-across hypothesis.

0.1.1.4. Adequacy and reliability of studies

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

(1) be adequate for the purpose of classification and labelling and/or risk assessment;
(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement.

27 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement sections 1-8. Therefore, no reliable predictions can be made for these information requirements.

0.1.2. Conclusion on the read-across approach

28 For the reasons 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 under Annex XI, Section 1.5. is rejected.

29 In your comments to the draft decision, you note your intention to improve the read-across justification, but you have not provided any further information. You remain responsible for complying with this decision by the set deadline.

Reasons related to the information under Annex VII of REACH

1. In vitro gene mutation study in bacteria

30 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

1.1. Information provided

31 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances:

(i) OECD TG 471 study (1989) with the analogue substance n-hexane, EC No. 203-777-62;

(ii) OECD TG 471 study (1999) with the analogue substance n-hexane, EC No. 203-777-62.

1.2. Assessment of information provided

32 We have assessed this information and identified the following issues:

1.2.1. Read-across adaptation rejected

33 As explained in Section 0.1., 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 below.

1.2.2. Adequacy and reliability of studies on the source substance

34 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 471. Therefore, the following specifications must be met:

a) the test is 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 induces 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 corresponds to 5 mg/plate or 5 µl/plate;
c) at least 5 doses are evaluated, in each test condition;
d) one positive control is included in the study and the positive control substance produces a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control;
e) the mean number of revertant colonies per plate is reported for the treated doses and the controls.

35 Studies (i) and (ii) are described as *in vitro* gene mutation studies in bacteria.

36 However, the following specifications are not according to the requirements of the OECD TG 471:

a) study (i) was performed with the strains S. typhimurium TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and study (ii) with S. typhimurium TA 98, TA 100, TA 1535 and TA 1537 (i.e., the strain E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102. is missing in both studies);
b) the maximum dose tested in study (ii) was 1000 µg/plate (i.e. less than 5 mg/plate or 5 ml/plate) and there is no indication in the dossier that this dose induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance;
c) there is no information on the levels and number of doses evaluated in study (ii);
d) there is no information on the positive and negative controls in study (ii);
e) the mean number of revertant colonies per plate for the treated doses and the controls was not reported in study (ii).

37 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

38 In your comments to the draft decision, you note your intention to provide additional information to address the above adequacy and reliability issues. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

1.3. Specification of the study design

40 To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

2. Ready biodegradability

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

2.1. Information provided

42 You have adapted this information requirement by using Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) and a Grouping of substances and read-across approach based on data from the following substances:

(i) a ready biodegradability study (OECD TG 301C, 2002) with the analogue substance 2-methylpentane, EC No. 203-523-4;

(ii) QSAR predition on ready biodegradability (EPIWIN, EPI suite 4.11, 2012) with the Substance.

2.2. Assessment of information provided

43 We have assessed this information and identified the following issues:

2.2.1. Read-across adaptation rejected

44 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

2.2.2. Validity of the QSAR results

45 REACH Guidance Chapter R.6.1.3.2 specifies that the regulatory relevance of a (Q)SAR expresses the usefulness of the predicted endpoint in relation to the information needed for the regulatory purpose.

46 ECHA Practical Guide on How to use and report (Q)SARs Chapter 3.3 specifies that results from (Q)SAR models are adequate for risk assessment or classification and labelling when they are equivalent to results obtained from the required experimental test. For this information requirement, the test method is OECD TG 301, which measures ready biodegradability in terms of ultimate biodegradation (as percentage of dissolved organic carbon removal, theoretical carbon dioxide, or theoretical oxigen demand).

47 You have provided the prediction from the (Q)SAR model BIOHCWIN, which predicts the primary biodegradation half-life in days.

48 The prediction from BIOHC model does not include information on ultimate biodegradation, which is necessary to assess the ready biodegradability of the Substance. Therefore, the prediction is not adequate to meet the information requirement for ready biodegradability for the purpose of classification and labelling and/or risk assessment.

49 In your comments, you stated that information on a ready biodegradability study (OECD 301C) on the Substance is available and that you will provide this information in an update of your registration dossier. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

Reasons related to the information under Annex VIII of REACH

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

51 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.

3.1. Information provided

52 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances:

(i) OECD TG 473 study (1994) with the analogue substance n-hexane, EC No. 203-777-62.

3.2. Assessment of information provided

53 We have assessed this information and identified the following issues:

3.2.1. Read-across adaptation rejected

54 As explained in Section 0.1, 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 below.

3.2.2. Adequacy and reliability of study on the source substance

55 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 473 or OECD TG 487. Therefore, the following specifications must be met:

a) at least 300 well-spread metaphases are scored per concentration.

56 Study (i) is described as *in vitro* chromosomal aberration study in mammalian cells.

57 However, the following specifications are not according to the requirements of the OECD TG 473:

a) 100 metaphases (i.e., less than 300 metaphases) were scored per concentration.

58 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

59 In your comments to the draft decision, you stated that information on an *in vitro* cytogenicity study (OECD TG 473) with the Substance is available and that you will provide this information in an update of your registration dossier. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

3.3. Specification of the study design

61 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.

4. In vitro gene mutation study in mammalian cells

62 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.

4.1. Triggering of the information requirement

63 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.

64 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 requests 1 and 3.

65 The result of the requests for an *in vitro* gene mutation study in bacteria and for an *in vitro* cytogenicity study or *in vitro* micronucleus study in mammalian cells or *in vitro* micronucleus study 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.

66 Consequently, you are required to provide information for this information requirement, 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.

4.2. Information provided

67 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances:

(i) OECD TG 476 study (1990) with the analogue substance n-hexane, EC No. 203-777-62.

4.3. Assessment of information provided

68 We have assessed this information and identified the following issues:

4.3.1. Read-across adaptation rejected

69 As explained in Section 0.1, 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 below.

4.3.2. Adequacy and reliability of study on the source substance

70 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a

particular information requirement, in this case OECD TG 476 or OECD TG 490. Therefore, the following specifications must be met:

a) the maximum concentration tested induces 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 corresponds to 10 mM, 2 mg/mL or 2 µL/mL, whichever is the lowest;

71 The study (i) is described as an *in vitro* gene mutation study in mammalian cells.

72 The maximum tested concentration in study (i) was 0.132 µL/mL with and without metabolic activation in the absence of reported precipitation.

73 You indicate that the test substance was cytotoxic at concentrations of 0.063 µL/mL or greater without assessing whether it was inducing 80-90% cytotoxicity. However, the cloning efficiency was only slightly affected by the treatment and was between 0.85 and 1.06 with metabolic activation (1.00 at the maximum tested concentration) vs. 1.10 for the solvent control, and between 0.87 and 1.07 without metabolic activation (0.95 at the maximum tested concentration) vs. 1.10 for the solvent control.

74 However, the following specifications are not according to the requirements of the OECD TG 476/490:

a) the maximum tested concentration did not induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance, and it was less than 10 mM, 2 mg/mL or 2 µL/mL.

75 Therefore, the studies submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

76 In your comments to the draft decision, you stated that information on an *in vivo* micronucleus study (OECD TG 474) with the Substance is available and that you will provide this information in an update of your registration dossier to adapt the information requirement for an *in vitro* gene mutation study in mammalian cells. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment. However, ECHA notes that the *in vivo* micronucleus study (OECD TG 474) investigates chromosomal aberration and not gene mutation. Therefore, it cannot be used under Annex VIII, Section 8.4.3., Column 2, which specifies that the *in vitro* gene mutation study in mammalian cells may be omitted if adequate data from a reliable *in vivo* mammalian gene mutation test are available.

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

4.4. Specification of the study design

78 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.

5. Short-term repeated dose toxicity (28 days)

79 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1.

5.1. Information provided

80 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances:

(i) OECD TG 413 study in rats (1990a) with the analogue substance n-hexane, EC No. 203-777-62;

(ii) OECD TG 413 study in mice (1990b) with the analogue substance n-hexane, EC No. 203-777-62;

(iii) Non-guideline sub-chronic toxicity study through inhalation in rats (1983a) with the analogue substance Hydrocarbons, C6, n-alkanes, isoalkanes, cyclics, *n*-hexane rich, List No. 925-292-5 ("mixed hexanes");

(iv) Non-guideline sub-chronic toxicity study through inhalation in rats (1983b) with the analogue substance Hydrocarbons, C6, n-alkanes, isoalkanes, cyclics, *n*-hexane rich, List No. 925-292-5 ("mixed hexanes");

(v) Non-guideline neurotoxicity screening study through inhalation in rats (1999) with the analogue substance 2-methylpentane, EC No. 203-523-4.

5.2. Assessment of information provided

81 We have assessed this information and identified the following issue:

5.2.1. Read-across adaptation rejected

82 As explained in Section 0.1, 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 below.

5.2.2. Adequacy and reliability of study on the source substance

83 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 412. Therefore, the following specifications must be met:

a) testing of at least three dose levels (unless conducted at the limit dose) with concurrent controls;
b) haematological and clinical biochemistry tests as specified in paragraphs 48-49 of the test guideline;
c) gross pathology as specified in paragraphs 53-56 of the test guideline;
d) full histopathology as specified in paragraphs 57 of the test guideline.

84 The studies (iii)-(v) are described as a sub-chronic inhalation toxicity studies.

85 However, the following specifications are not according to the requirements of the OECD TG 412:

a) Only two dose levels were used in study (iii) and one dose level in study (v);
b) data on haematology and clinical biochemistry findings are missing in studies (iii), (iv) and (v).
c) data on gross pathology findings are missing in study (v) since it only investigated nerve samples;
d) data on histopathology findings are missing in study (v) since it only investigated

nerve samples.

86 Therefore, the studies (iii)-(v) submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

87 In your comments to the draft decision, you stated that information on a 90-day repeated dose toxicity study through inhalation (OECD TG 413) with the Substance is available and that you will provide this information in an update of your registration dossier to adapt the information requirement for a 28-day repeated dose toxicity study. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

5.3. Specification of the study design

89 Further information on the study design is provided under Section 6 below.

6. Screening for reproductive/developmental toxicity

90 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or *in vitro* methods that the substance may be a developmental toxicant.

6.1. Information provided

91 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances to fulfil an adaptation under Column 2:

(i) OECD TG 416 study through inhalation in rats (1994) with the analogue substance n-hexane, EC No. 203-777-62;

(ii) OECD TG 414 study through inhalation in mice (1989a) with the analogue substance n-hexane, EC No. 203-777-62;

(iii) OECD TG 414 study through inhalation in rats (1989b) with the analogue substance n-hexane, EC No. 203-777-62.

6.2. Assessment of information provided

92 We have assessed this information and identified the following issue:

6.2.1. Read-across adaptation rejected

93 As explained in Section 0.1, 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 below.

6.2.2. Adequacy and reliability of study on the source substance

94 Under Annex VIII, Section 8.7., Column 2, the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) is already available.

95 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study, in this case OECD TG 414. Therefore, the following specifications must be met:

a) the study is conducted in rats or rabbits; a justification should be provided if another species is used;
b) the nature, severity, and duration of the clinical signs are observed daily;
c) the dams are examined for any structural abnormalities, weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight, and uterine content.

96 However, the following specifications are not according to the requirements of the OECD TG 414:

a) the study (ii) was conducted in mice without justification;
b) data on clinical signs, including nature and severity, are missing;
c) data on the examination of the dams, including incidence and severity, are missing, in particular data on weight and histopathology of the thyroid gland, thyroid hormone measurements.

97 Therefore, the studies (ii) and (iii) submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

98 Based on the above, the provided study is not reliable and your adaptation is rejected.

99 In your comments to the draft decision, you note your intention to provide additional information to address the above adequacy and reliability issues. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

6.3. Specification of the study design

101 When there is no information available neither for the 28-day repeated dose toxicity endpoint (as explained above under Section 5), nor for the screening study for reproductive/ developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day repeated dose toxicity study, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[2]

102 A study according to the test method EU B.64/OECD TG 422 must be performed in rats.

103 The study must be conducted with inhalation exposure of the Substance because the Substance is a volatile liquid with a vapour pressure of 150 hPa at 20°C (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

104 Therefore, the study must be conducted in rats with inhalation exposure of the Substance.

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)

7. Short-term toxicity testing on fish

105 Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

7.1. Information provided

106 You have adapted this information requirement by using a Grouping of substances and read-across approach based on data from the following substances:

(i) a study on short-term toxicity to fish (publication, 1986) with the analogue substance *n*-hexane, EC No. 203-777-6;

(ii) QSAR prediction on short-term toxicity to fish ([redacted], 2009) with the analogue substance Hydrocarbons, C5 -C7, n-alkanes, isoalkanes, *n*-hexane rich, List No. 930-397-4;

(iii) QSAR prediction on short-term toxicity to fish ([redacted], 2009) with the analogue substance Hydrocarbons, C6, isoalkanes, <5% *n*-hexane, List No. 931-254-9;

(iv) QSAR prediction on short-term toxicity to fish ([redacted], 2009) with the analogue substance *n*-hexane, EC No. 203-777-6;

(v) QSAR prediction on short-term toxicity to fish ([redacted], 2009) with the analogue substance Hydrocarbons, C6, n-alkanes, isoalkanes, cyclics, *n*-hexane rich, List No. 925-292-5;

7.2. Assessment of the information provided

107 We have assessed this information and identified the following issues:

7.2.1. Read-across adaptation rejected

108 As explained in Section 0.1., 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 below.

7.2.2. Adequacy and reliability of study on the source substance

109 As explained in the Appendix on Reasons common to several requests, the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 203 and the requirements of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

110 Validity criteria

a) mortality in the control(s) is ≤ 10% (or one fish, if fewer than 10 control fish are tested) at the end of the test;
b) the dissolved oxygen concentration is ≥ 60% of the air saturation value in all test vessels throughout the exposure;
c) the analytical measurement of test concentrations is conducted;

111 Technical specifications impacting the sensitivity/reliability of the test

d) all fish are held in the laboratory for at least 9 days before being used for testing (including a 48 hours settling-in period and a 7 days acclimation period);
e) only batches showing mortalities below 5% of the population in seven days and with no diseases or abnormalities are used;
f) the test is conducted on juveniles of similar age (or size);
g) the test duration is 96 hours or longer;

112 Your registration dossier provides an OECD TG 203 study showing the following:

113 There is no information on the specifications a)-f) above. The test duration was 48 hours.

114 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically the test duration was too short, Therefore the study is not reliable.
- Furthermore, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. It is not possible to verify the validity criteria and the technical specifications impacting the sensitivity/reliability of the test.

115 Therefore, the requirements of OECD TG 203 are not met.

7.2.3. Adequacy and reliability of QSAR results on the source substances

116 As explained in the Appendix on Reasons common to several requests, the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

117 Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid and thus to be adequate for the purpose of classification and labelling and/or risk assessment. For that purpose, the fourth OECD principle requires that appropriate measures of the internal performance (i.e. goodness-of-fit and robustness using the learning data set) and predictivity (using a test data set) of the model are available.

118 You used the [redacted] tool to predict short term toxicity to fish. Reference is made to the report "[redacted]" by [redacted], from 2009.

119 The [redacted] model has a number of shortcomings in the target lipid model which likely lead to an underestimation of the (environmental) risk related to the production and use of petroleum products.[3] These shortcomings are not addressed in your justification.

120 On that basis, we conclude that the scientific validity of the model has not been established, and there is a risk of underestimating toxicity. Therefore, the information provided is not adequate for the purpose of classification and labelling and/or risk assessment.

121 In your comments, you stated that information on a short-term toxicity on fish study (OECD 203) on the Substance is available and that you will provide this information in an update of your registration dossier. As no details were provided, the information in your comments is not sufficient for ECHA to make an assessment.

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

7.3. Study design and test specifications

[3] https://echa.europa.eu/documents/10162/17221/review_environmental_physicochemical_methodol_en.pdf/5057f972-041b-4813-8287-28bf33f65b11?t=1382363028262

123 The Substance is difficult to test due to the high volatility (vapour pressure of 150 hPa at 20 °C). OECD TG 203 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 203. 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 solutions.

8. Adsorption/ desorption screening

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

8.1. Information provided

125 You have adapted this information requirement by using and a Grouping of substances and read-across approach based on data from the following substance:

(i) QSAR predition on adsorption/desorption (QSARs for soil sorption, 1995) with the analogue substance *n*-hexane, EC No. 203-777-6;

8.2. Assessment of the information provided

126 We have assessed this information and identified the following issue:

8.2.1. Read-across adaptation rejected

127 As explained in Section 0.1, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

128 In your comments, you agree to perform the study on the Substance.

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

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).

All Guidance on REACH is 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 15 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).

In your comments on the draft decision, you also requested an extension of the deadline to provide information from 12 to 24 months from the date of adoption of the decision.

On this basis, ECHA has granted the request and exceptionally extended the deadline by 12 months from the standard deadline 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: Addressees 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]

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 summaries[4].

(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.

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

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