~~Confidential~~

Helsinki, 10 February 2022

Addressees
Registrant(s) of JS-2-Methylpyridine as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
13/06/2016

Registered substance subject to this decision ("the Substance")
Substance name: 2-methylpyridine
EC number: 203-643-7
CAS number: 109-06-8

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 ***15 November 2024***.

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

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

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

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

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

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

2. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

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

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

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

Information required depends on your tonnage band

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

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

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

How to comply with your information requirements

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

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

Appeal

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

Failure to comply

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

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

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

Appendix on Reasons common to several requests

1. **Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.**

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

- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

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

Grouping of substances and read-across approach

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

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

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group (category) of '*pyridine and alkyl pyridine derivatives comprised of: pyridine (CAS 110-86-1), 2-methylpyridine (CAS 109-06-8), 3-Methylpyridine (CAS 108-99-6), and 4-Methylpyridine (CAS 108-89-4)*'. You have provided a read-across justification document in IUCLID Section 13.1, i.e. CSR.

For the purpose of this decision, the following abbreviations are used for the group members:
[1] *Pyridine (EC* 203-809-9*)*;
[2] *the Substance,* 2-Methylpyridine (EC- 203-643-7);
[3] *3-Methylpyridine (EC* 203-636-9*);*
[4] *4-Methylpyridine (EC-* 202-852-0*).*

You define the applicability domain of the category as follows: *"pyridine unsaturated ring as common functional group and similar physical porperties environmental fate and toxicity, and mammalian toxicity"*. ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

B. Predictions for properties

a. Prediction for toxicological properties

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

You provide the following reasoning for the grouping the substances: "*A category of pyridine and alkyl pyridine derivatives is comprised of: pyridine (CAS 110-86-1), 2-methylpyridine (CAS 109-06-8), 3-Methylpyridine (CAS 108-99-6), and 4-Methylpyridine (CAS 108-89-4). The foundation of the category is a common functional group (the pyridine unsaturated ring structure) and similar physical properties, environmental fate and toxicity, and mammalian toxicity. Similar toxicological properties derive from physical-chemical parameters and common pathways of metabolism and elimination among all members of the category.*
The U.S. Environmental Protection Agency has accepted this category, as indicated in its September 2009 Hazard Characterization Document reviewing the screening-level data set submitted by an industry consortium under the voluntary High Production Volume (HPV) Program. In this 2009 document, this group of substances is referred to as Sub-category I, to differentiate it from other pyridine derivatives including nitriles and piperidine."

You intend to predict the properties for the category members from information obtained from the following source substances:

Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)

[1] Pyridine, EC-203-809-9;
[3] *3-Methylpyridine*, EC-203-636-9;

Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

[1] Pyridine, EC-203-809-9;
[3] *3-Methylpyridine*, EC-203-636-9;

We note the following deficiencies with regards to prediction of toxicological properties.

1. *Missing supporting information to compare properties between substances*

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose, "*it is important to provide supporting information to strengthen the rationale for the read-across*"[4]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s). Supporting information must include bridging studies to compare properties of the category members.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar category members cause the same type of effect(s). In this context, relevant, reliable, and adequate information allowing to compare the properties of the category members is necessary to confirm that both substances cause the same type of

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

effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the category members.

You have provided information only on the category members [1] and [3]. The data set reported in the technical dossier does not include relevant, reliable, and adequate information for the category members [2] and [4] to support your read-across hypothesis.

We conclude that there is no study with the Substance available for repeated dose toxicity and reproductive/developmental toxicity that would allow to compare its effects with that of the source substance(s).

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 strengthen the rationale for the read-across.

2. Adequacy and reliability of source study

In accordance with Annex XI, Section 1.5., if grouping concept is applied then in all cases, the results should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

According to the provisions of Annex VIII, Section 8.7.1., information on Screening for reproductive and developmental toxicity as specified in the OECD TG 421/422 must be provided. The identified deficiencies are explained in section B.3.

b. Predictions for ecotoxicological properties

You have provided the following reasoning for the prediction of aquatic toxicity:
"The foundation of the category is a common functional group (the pyridine unsaturated ring structure) and similar physical properties, environmental fate and toxicity, and mammalian toxicity".

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

You intend to predict the properties for the Substance from information obtained from 3-Methylpyridine (EC No. 203-636-9) as source substance for the following endpoints:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

We note the following shortcomings with regards to prediction of aquatic toxicity.

1. Read-across hypothesis

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[5]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

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

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and toxicological properties between the category members is a sufficient basis for predicting the properties of the Substance for other endpoints.

However, there are structural differences between the source and target substances. The source substance has a [redacted]. The activity of certain classes of organic chemicals may differ based on the substitution position on the ring. Ortho, meta, and para substituents on the ring are expected to have different stability and also different (eco)toxicological outcomes. The pyridine ring is a weak base with an aromatic character. Electron-donating substituents like methyl groups can be expected to make pyridine derivatives more basic. Moreover, the basicity of the substituted pyridine is expected to be dependent on the position of the substituent on the ring. You have not explained why these differences would not imply that the (eco)toxicological effects differ between the target and source substances. Therefore, you have not demonstrated that it is possible to derive a reliable prediction for (eco)toxicological properties, based on recognition of the structural differences between the target and source substances.

Furthermore, similarity of some of the physicochemical and toxicological properties would not necessarily lead to predictable or similar ecotoxicological properties.

Therefore, you have not provided a well-founded hypothesis to establish a reliable prediction for the ecotoxicological properties.

2. Adequacy and reliability of source study

In accordance with Annex XI, Section 1.5., if a grouping concept is applied then in all cases, the results should have adequate and reliable coverage of the key parameters addressed in the corresponding test methods referred to in Article 13(3).

The source studies that you have used in your read-across approach for the prediction of aquatic toxicity have critical deficiencies. Those deficiencies are explained below in sections A.1, A.2 and B.4. for respectively: short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.), growth inhibition study aquatic plants (Annex VII, Section 9.1.2.), and short-term toxicity testing on fish (Annex VIII, Section 9.1.3.).

C. Conclusions on the grouping of substances and read-across approach

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

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

1. Short-term toxicity testing on aquatic invertebrates

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

You have provided the following information:

i. 1991, a key study performed with read-across substance 3-methylpyridine (EC No. 203-636-9);
ii. 2008, a supporting study performed with the Substance.

We have assessed this information and identified the following issues:

As explained in the Appendix on general considerations, your read-across adaptation is rejected (study i).

In addition, ECHA has identified the following endpoint-specific deficiencies with study (i) as well as deficiencies with study (ii) which ECHA understands was submitted under Section 1.1.2 of Annex XI:

Furthermore, in order to fulfil the information requirement, a study must comply with:

- Annex XI, Section 1.5 if a read-across approach is used. As explained under the Appendix on reasons common to several requests, the study must have adequate and reliable coverage of the key parameters of OECD 202; or
- Annex XI, Section 1.1.2 if the study was performed on the Substance before 1 June 2008. According to that Annex, the study must have adequate and reliable coverage of the key parameters of OECD 202.

If the substance is difficult to test, the studies must in addition comply with the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1).

In particular, the following specifications must be met:

Validity criteria

- the percentage of immobilised daphnids is ≤ 10% at the end of the test in the controls (including the solvent control, if applicable);
- the dissolved oxygen concentration is ≥ 3 mg/L in all test vessels at the end of the test;

Technical specifications impacting the sensitivity/reliability of the test

- the test duration is 48 hours or longer;
- young daphnids, aged less than 24 hours at the start of the test, are used;
- test animals are not fed during the test;
- at least 20 animals are used at each test concentration and for the controls;
- the test temperature is within 18°C to 22°C and does not vary by over ±1°C;
- the test medium fulfils the following condition(s): particulate matter ≤ 20 mg/L, total organic carbon (TOC) ≤ 2 mg/L, hardness between 140 and 250 mg/L (as $CaCO_3$), pH between 6 and 9;
- at least five concentrations are tested. If less than five concentrations are included in the test design a justification must be provided;
- test concentrations follow a geometric series with a spacing factor < 2.2;

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
- the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1)

Validity criteria

For study ii, no information is provided on:

- the percentage of immobilised daphnids at the end of the test in the controls;
- the dissolved oxygen concentration at the end of the test;

Technical specifications impacting the sensitivity/reliability of the test

For study ii, no information is provided on:

- the age of the test animals;
- whether they were fed during the test;
- the number of test animals used for each test concentration and for the controls;
- the test temperature;
- the test medium;
- the test concentrations.

Furthermore, the test duration was 24 hours for study ii.

As for the key study (study i), no analytical monitoring of exposure was conducted.

The Substance is difficult to test due to the high vapour pressure (vapour pressure values ranging from 949 to 1333 Pa at 20 -24.4 °C). The studies (2008) on *Daphnia* or on algae show an important difference between nominal and measured concentrations (around a factor of 2) for the Substance, suggesting that important losses can occur when testing the Substance.

Based on the above, there are critical deficiencies for both studies, resulting in the rejection of their results:

- the validity criteria of OECD TG 202 and the reliability of the test cannot be verified for study ii;
- the test duration for the supporting study (study ii) was too short and other important information for assessing the reliability of that study is missing;
- analytical monitoring of exposure was not conducted for the key study (study i).

Therefore, you have not demonstrated that the requirements of OECD TG 202 are met or adequate and reliable coverage of the key parameters of that TG.

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

Study design

The Substance is difficult to test. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible

to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2. Growth inhibition study aquatic plants

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

You have provided the following information:

i. A key study performed with read-across substance 3-methylpyridine (EC No. 203-636-9) in 1991;
ii. A supporting study, performed with the Substance in 2008;
iii. A supporting study performed with the Substance in 2005.

We have assessed this information and identified the following issues:

As explained in the Appendix on general considerations, your read-across adaptation is rejected (study i).

In addition, ECHA has identified the following endpoint-specific deficiencies with study (i) as well as deficiencies with study (iii) which ECHA understands was submitted under Section 1.1.2 of Annex XI, and study (ii):

Furthermore, in order to fulfil the information requirement, a study must comply with:

- OECD TG 201 for study on the Substance conducted after 1 June 2008 (Article 13(3) of REACH); or
- Annex XI, Section 1.5 if a read-across approach is used. As explained under the Appendix on reasons common to several requests, the study must have adequate and reliable coverage of the key parameters of OECD 201; or
- Annex XI, Section 1.1.2 if the study was performed on the Substance before 1 June 2008. According to that Annex, the study must have adequate and reliable coverage of the key parameters of OECD 201.

If the substance is difficult to test, the studies must in addition comply with the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1).

In particular, the following specifications must be met:

Key parameters to be measured

- 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;

Validity criteria

- exponential growth in the control cultures is observed over the entire duration of the test;
- at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
- 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 ≤ 35%;
- the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with *Pseudokirchneriella subcapitata* or

Desmodesmus subspicatus. For other less frequently tested species, the value is ≤ 10%;

Technical specifications impacting the sensitivity/reliability of the test

- the test duration is 72 hours. For slow-growing species (*i.e.* specific growth rate < 0.92 day^{-1} in the control), the test duration must be extended until the biomass in the control cultures increases by at least 16-fold;
- three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;
- one of the two alternative growth medium (*i.e.* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified;
- the pH of the control medium does not increase by > 1.5 units;

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
- the test media prepared specifically for analysis of exposure concentrations during the test is treated identically to those used for testing (*i.e.* inoculated with algae and incubated under identical conditions);
- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

  For volatile, unstable or strongly adsorbing test substances, additional samplings for analysis at 24-hour intervals are required.
- the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within 20 % of the nominal or measured initial concentration throughout the test;
- if the concentration of the test material has not been maintained within 20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material.

Your registration dossier provides three studies showing the following:

Key parameters to be measured

No NOEC or EC10 is provided (studies i, ii and iii).

Validity criteria

No information is provided on:

- the section-by-section growth rates in the control cultures (studies i, ii and iii);
- the initial biomass and the biomass in the control at the end of the test (studies ii and iii);
- the mean coefficient of variation for section-by-section specific growth in the control (studies i, ii and iii);
- the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures (studies i, ii and iii).

Technical specifications impacting the sensitivity/reliability of the test

No information is provided on:

- the number of replicates (studies ii and iii);

- the test medium (study ii). For study i, the test medium is described as a "Boltz Basal Medium" whereas for study iii, the test medium is described as a "BG11 medium". However, you have not provided a justification as why one of the two alternative growth medium of OECD TG 201 was not used;
- the pH increase in the controls (studies ii and iii).

For study iii, the test duration is 14 days but there is no information on the specific growth rate in the control. There is no information on whether exponential growth was maintained in the control cultures over the entire duration of that test.

Characterisation of exposure

No analytical monitoring of exposure was conducted for studies i and iii. For those two studies, the results are based on nominal concentrations.

The Substance is difficult to test due to the high vapour pressure (vapour pressure values ranging from 949 to 1333 Pa at 20 -24.4 °C). The studies of (2008) on *Daphnia* or on algae show an important difference between nominal and measured concentrations (around a factor of 2) for the Substance, suggesting that important losses can occur when testing the Substance.

Based on the above, there are critical deficiencies for the three studies, resulting in the rejection of their results:

- the key parameters of OECD TG 201 are not covered (studies i, ii and iii);
- the validity criteria of OECD TG 201 cannot be verified (studies i, ii and iii);
- important information on the technical specifications of the tests is missing for assessing their reliability;
- for studies i and iii, analytical monitoring of exposure was not conducted, and you have not demonstrated that the concentration of the test material was satisfactorily maintained within 20 % of the nominal concentrations throughout the test. The Substance has a high vapour pressure (vapour pressure values ranging from 949 to 1333 Pa at 20 -24.4 °C) and therefore may have volatilised from the test medium. Study ii, for which analytical monitoring of exposure was performed, shows an important difference between nominal and measured concentrations (almost a factor of 2) for the Substance, suggesting that important losses can occur when testing the Substance.

Therefore, you have not demonstrated that the requirements of OECD TG 201 are met or adequate and reliable coverage of the key parameters of that TG.

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

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

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

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

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

You have provided a key study in your dossier:

i. 1993, DNA single strand breaks test with the Substance.

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

To fulfil the information requirement, a study must be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells and comply with the OECD TG 473 or OECD TG 487 (Article 13(3) of REACH and ECHA Guidance R.7, Table R.7.7-2).

The information provided is not an *in vitro* cytogenicity study in mammalian cells nor an *in vitro* micronucleus study. Therefore, the information provided does not cover the key parameter(s) required by the OECD TG 473/487.

Therefore, the information requirement is not fulfilled.

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

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have provided an adaptation according to Annex XI, Section 1.5. in your dossier.
In support of your adaptation you have submitted the following studies:

(i) 2003, mice, OECD Combined Toxicity/Carcinogenicity Guideline 453 with the analogue substance [3];
(ii) 1987, SD rat similar to OECD 408, with the analogue substance [1];
(iii) 2006, Wistar or F344 rat, Chronic combined oral toxicity/carcinogenicity (similar to OECD TG 453) with the analogue substance [3];
(iv) 1991, Wistar or F344 rat, 2 year combined repeated dose and carcinogenicity study (according to EPA OTS 798.3260 Chronic Toxicity) with the analogue substance [1];
(v) 2006, mice, similar to OECD combined toxicity/carcinogenicity TG 453, with the analogue substance [3];
(vi) 1990, Wistar or F344 rat, according to EPA OPPTS 870.3100 (90-Day Oral Toxicity in Rodents) with the analogue substance [1];
(vii) 2003, Fischer 344 rat, according to EPA OPPTS 870.3100 (90-Day Oral Toxicity in Rodents) with the analogue substance [3];
(viii) 1990, Wistar or F344 rat, according to EPA OPPTS 870.3100 (90-Day Oral Toxicity in Rodents) with the analogue substance [1];
(ix) 1993, Wistar rat or F344 rat, according to EPA OTS 798.3260 (Chronic Toxicity), with the analogue substance [1];
(x) 1984, rat, inhalation, similar to OECD Guideline 412 (Subacute Inhalation Toxicity: 28-Day Study) with the analogue substance [3].

We have evaluated the information and identified the following issue.

As explained in the Appendix common to several request your adaptation is rejected. In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

As explained in the Appendix on reasons common to several requests, if the grouping concept is applied then in all cases, the results should have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 407. The key parameter(s) of this test guideline include dosing of the Substance daily for a period of 28 days until the scheduled termination of the study

The study (x) you have provided does not have the required exposure duration of 28 days as required in OECD TG 407, because you indicated an exposure duration of 14 days.

Therefore, the study does not fulfil the key parameters set in OECD TG 407.

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

Information on the design of the study to be performed (route/ species/ strain)

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), 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 study according to OECD TG 407, 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.[6]

Referring to the criteria in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because although the information indicate that human exposure to the Substance by the inhalation route is likely, further information on repeated dose toxicity by the oral route is needed to be able to conclude on systemic toxicity for the substance. We acknowledge, although read-across for the purpose of fulfilling information requirements is rejected for the reasons explained in the first Appendix, the indications of hazard observed via the oral route of an analogue substance lead to a concern as the two substances are structurally similar and the information available does not exclude that the observed hazards are caused by this similar structure. Hence, the test shall be performed by the oral route using the test method OECD TG 422.

According to the test method OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route (gavage).

3. Screening for reproductive/developmental toxicity

Screening for reproductive/developmental toxicity is a standard information requirement under Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided an adaptation according to Annex XI, Section 1.5. in your dossier.

[6] ECHA Guidance, 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)

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

In support of your adaptation you have submitted the following studies:

(i) 2004, B6C3F1 mice, OECD Combined Toxicity/Carcinogenicity (similar to OECD TG 453) with the analogue substance [3];
(ii) 2004, F344 rat, Chronic combined oral toxicity/carcinogenicity (similar to OECD TG 453) with the analogue substance [3];
(iii) 2000 (performed in 1991 and 1993), Wistar and F344 rat, 2 year combined repeated dose and carcinogenicity study (according to EPA OTS 798.3260 Chronic Toxicity) with the analogue substance [1];
(iv) 2008, Reproduction/Developmental Toxicity Screening Test (according to OECD 421) with the analogue substance [1].

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

As explained in the Appendix common to several request your adaptation is rejected. In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

As explained in the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding TG, in this case the study has to meet the requirements of EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

We have identified the following endpoint-specific deficiencies for the source studies (i) – (iii) in your read-across adaptation.

The key parameters of EU B.63/OECD TG 421 or EU B.64/OECD TG 422 include for example

- Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation
- Examination of key parameters for toxicity such as clinical signs/body weight/body weight changes/food consumption/thyroid hormone assessment (P0 and F1)
- Examination of parameters for sexual function and fertility such as /those for mating and fertility/duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues
- Monitoring of oestrus cycles
- Examination of offspring parameters such as /number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/number of nipples/areolae in male pups

The provided study (i) – (iii) lack the following key parameters:

- Dosing of the Substance for approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation
- Examination of key parameters for toxicity such as clinical signs/body weight/body weight changes/food consumption/thyroid hormone assessment (F1)
- Examination of parameters for sexual function and fertility such as /those for mating and fertility/duration of gestation, parturition, lactation and weight and histopathology of reproductive organs and tissues
- Monitoring of oestrus cycles
- Examination of offspring parameters such as /number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/number of nipples/areolae in male pups.

Therefore, studies (i) – (iii) do not fulfil all key parameters of EU B.63/OECD TG 421 or EU B.64/OECD TG 422.

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

Information on study design

As explained under request B.1 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 study according to OECD TG 407, 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.[7]

According to the test methods OECD TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit information derived with the registered substance subject to the present decision: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route (gavage).

2. Short-term toxicity testing on fish

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

You have provided the following information:

i. a key study performed with read-across substance 3-methylpyridine (EC No. 203-636-9) in 1991;
ii. a supporting study performed with the Substance in 1986.

We have assessed this information and identified the following issues:

As explained in the Appendix on general considerations, your read-across adaptation is rejected (study i).

In addition, ECHA has identified the following endpoint-specific deficiencies with study (i) as well as deficiencies with study (ii) which ECHA understands was submitted under Section 1.1.2 of Annex XI:

Furthermore, in order to fulfil the information requirement, a study must comply with:

- Annex XI, Section 1.5 if a read-across approach is used. As explained under the Appendix on reasons common to several requests, the study must have adequate and reliable coverage of the key parameters of OECD 203; or
- Annex XI, Section 1.1.2 if the study was performed on the Substance before 1 June 2008. According to that Annex, the study must have adequate and reliable coverage of the key parameters of OECD 203.

If the substance is difficult to test, the studies must in addition comply with the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1).

In particular, the following specifications must be met:

[7] ECHA Guidance, 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)

Validity criteria

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

Technical specifications impacting the sensitivity/reliability of the test

- 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). Only batches showing mortalities below 5% of the population in seven days and with no diseases or abnormalities are used;
- the test is conducted on juveniles of similar age (or size);
- at least 7 fish are used at each test concentration and in the control(s);
- at least 5 concentrations are tested;
- the concentrations are arranged in a geometric series with a spacing factor ≤ 2.2.

Your registration dossier provides two studies showing the following:

Validity criteria

For the key study (study i), no analytical measurement of test concentrations was conducted. For the supporting study (study ii), no information is provided on mortality in the controls.

Technical specifications impacting the sensitivity/reliability of the test

For the supporting study (study ii), the reporting is not sufficient to conduct an independent assessment of its reliability. In particular, no information is provided on:

- whether the fish were acclimatised before the start of the test;
- the age or size of the fish;
- the number of fish used for each test concentration and for the controls;
- the test concentrations.

The Substance is difficult to test due to the high vapour pressure (vapour pressure values ranging from 949 to 1333 Pa at 20 -24.4 °C). The studies of (2008) on *Daphnia* or on algae show an important difference between nominal and measured concentrations (around a factor of 2) for the Substance, suggesting that important losses can occur when testing the Substance.

Based on the above, there are critical deficiencies for both studies, resulting in the rejection of their results:

- for the key study (study i), no analytical monitoring of exposure was conducted. Therefore, one of the validity criteria of OECD TG 203 is not met;
- for the supporting study (study ii) the reporting is not sufficient to assess the validity criteria of OECD TG 203 and the reliability of the test.

Therefore, you have not demonstrated adequate and reliable coverage of the key parameters of OECD TG 203.

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

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

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

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[8].

B. Test material

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

1. Selection of the Test material(s)

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

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

Appendix D: Procedure

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

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

The compliance check was initiated on 9 November 2020.

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

In your comments on the initial draft decision you commented on the deadline by indicating that meeting the schedule could be challenging. However, you did not provide any proof for an extension need.

ECHA took into account your comments and did not amend the deadline.

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

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

Appendix E: List of references - ECHA Guidance[10] and other supporting documents

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

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

Read-across assessment framework (RAAF, March 2017)[11]

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

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

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

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

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

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

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

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

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

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

OECD Guidance documents[13]

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

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

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

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

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

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

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

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