~~Confidential~~

Helsinki, 10 February 2022

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

Date of submission of the dossier subject to this decision
12/05/2016

Registered substance subject to this decision ("the Substance")
Substance name: Pyridine
EC number: 203-809-9
CAS number: 110-86-1

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

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

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

2. Extended one-generation reproductive toxicity study (triggered by Annex IX, Section 8.7.3., column 1; test method: OECD TG 443) by oral route, in rats, specified as follows:

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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

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

D. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rat or rabbit)

2. Extended one-generation reproductive toxicity study also requested above (Annex X, Section 8.7.3.)

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

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to X 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 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.

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 your 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 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

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.

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".*

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.

B. Predictions for ecotoxicological properties

You have provided the following reasoning for the prediction of aquatic toxicity:

[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

"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".

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

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.)

ECHA notes the following shortcoming with regard to prediction(s) 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[4]. 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.

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 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 in other endpoints.

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).

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

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.1 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 adapted this information requirement by using a read-across approach under Annex XI, Section 1.5.

In support of your adaptation you have submitted a study performed with the read-across substance 3-methylpyridine (EC No. 203-636-9) in 1991.

We have assessed this information and identified the following issues:

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

As explained under the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters of the corresponding test method, in this case OECD 202. It must also meet the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test.

In particular, the following specifications must be met for the 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).

In the study provided in your registration dossier, no analytical monitoring of exposure was conducted, and the effect value is based on nominal concentration.

The Substance is difficult to test due to the high vapour pressure (vapour pressure of 2670 Pa at 20°C)

Based on the above, there are critical methodological deficiencies resulting in the rejection of the study results. Since no analytical monitoring of exposure was conducted in that study, you have not demonstrated that the concentration of the test material was satisfactorily maintained within 20 % of the nominal concentrations throughout the test.

Therefore, you have not demonstrated adequate and reliable coverage of the key parameters of OECD TG 202.

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

Study design

The Substance is difficult to test due to the high vapour pressure. 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.

In your comments to the initial draft decision you agree to perform the Long-term toxicity test on aquatic invertebrates according to the OECD TG 211 with the Substance, instead of Short-term toxicity study on aquatic invertebrates (OECD TG 202).

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 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 for the key study (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, 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 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 is 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 two studies showing the following:

Key parameters to be measured

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

Validity criteria

No information is provided on:

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

Technical specifications impacting the sensitivity/reliability of the test

No information is provided on:

- the number of replicates (study ii);
- the pH increase in the controls (study ii).

For study i, the test medium is described as a "Boltz Basal Medium" whereas for study ii, the test medium is described as a "BG11 medium". However, you have not provided a justification as why one of the two alternative growth media of OECD TG 201 was not used.

For the supporting study (study ii), 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 ii. 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 of 2670 Pa at 20°C)

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

- some of the key parameters of OECD TG 201 are not covered (studies i, and ii);
- some of the validity criteria of OECD TG 201 cannot be verified (studies i, and ii);
- analytical monitoring of exposure was not conducted (studies i, and ii), and you have not demonstrated that the concentration of the test material was satisfactorily maintained within 20 % of the nominal concentrations throughout the tests. The Substance has a high vapour pressure (vapour pressure of 2670 Pa at 20°C) and therefore may have volatilised from the test media.

Therefore, you have not demonstrated adequate and reliable coverage of the key parameters of OECD TG 201.

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. 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 1995.

We have assessed this information and identified the following issues:

As explained in the Appendix on general considerations, your read-across adaptation is rejected for the key study (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, 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:

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:

- 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 of 2670 Pa at 20°C)

Based on the above,

- 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.

In your comments to the initial draft decision you agree to perform the Long-term toxicity test on fish according to the OECD TG 210 with the Substance, instead of Short-term toxicity study on fish (OECD TG 203).

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

1. Pre-natal developmental toxicity study in one species

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

You have provided:
(i) Reproduction/Developmental Toxicity Screening Test (2008), according to OECD 421, with the Substance;
(ii) a data waiver: *"According to Regulation (EC) No.1907/2006, Annex IX, 8.7.3, Column 1, a two-generation reproductive toxicity study is required if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. The Annex further states, in Column 2, that the decision on the need to perform a study at this tonnage level or higher should be based on the outcome of existing test data and all other relevant available data. As existing subchronic, chronic and reproductive toxicity data exists on this substance, with no adverse effects noted in the reproductive systems of parental animals nor adverse developmental effects in the offspring, the criteria for adaptation are met. There is insufficient scientific evidence to rationalize the conduct of an in vivo two-generation reproductive toxicity study on this substance, and so the requirement is waived."*

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

1) Screening study (i)

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species, e.g external, skeletal and visceral malformations and variations has to be investigated as described in OECD TG 414.

You have not provided information following OECD TG 414. Instead, you have provided a "reproduction/ developmental toxicity screening test" (OECD TG 421) study (i). This study does not inform on skeletal and visceral malformations and variations as required by OECD TG 414.

Therefore, this study does not fulfil the information requirement.

2) Data waiver

You have submitted a data waiver referring to the section *Annex IX* 8.7.3, column 1 and Column 2. These waiver possibilities do not apply to a pre-natal developmental toxicity study in a first species.

Furthermore, assuming that you submitted an adaptation under Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, namely:
1) that there is no evidence of toxicity seen in any of the tests available and
2) that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and
3) that there is no or no significant human exposure.

In your adaptation, you have not substantiated your claim of *no toxicological activity* concerning reproductive performance, because e.g. estrous cycle length of high dose F344 females was significantly longer than that of the controls in the repeated dose toxicity study (see study (i) section D.2). Effects were as well observed in the above listed screening study (i). Secondly in your dossier you provide information on systemic absorption: *"[…Pyridine and*

its methyl derivatives are absorbed during inhalation, oral and dermal exposures. They are distributed into the body water compartment as evidenced by the finding of the highest levels in the kidney and being eliminated primarily in the urine...]." Thirdly, the uses indicate that humans are exposed at industrial sites and in laboratories.

Therefore, we conclude that none of the concomitant criteria listed above are met in this case.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[5] administration of the Substance.

2. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex IX to REACH, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore column 2 defines the conditions under which the study design needs to be expanded.

You consider that no adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies, and/or that these studies did not reveal other concerns in relation with reproductive toxicity: *"According to Regulation (EC) No.1907/2006, Annex IX, 8.7.3, Column 1, a two-generation reproductive toxicity study is required if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. The Annex further states, in Column 2, that the decision on the need to perform a study at this tonnage level or higher should be based on the outcome of existing test data and all other relevant available data. As existing subchronic, chronic and reproductive toxicity data exists on this substance, with no adverse effects noted in the reproductive systems of parental animals nor adverse developmental effects in the offspring, the criteria for adaptation are met. There is insufficient scientific evidence to rationalize the conduct of an in vivo two-generation reproductive toxicity study on this substance, and so the requirement is waived."*

However, adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in available studies. More specifically, reduced number of corpea lutea graviditatis and implants are reported in the 2008 screening study (see study (iv) in section D.2). Furthermore, oestrous cycle lengths in the 2000 chronic toxicity study with F344 rats was significantly longer than in the control group (see study (i) section D.2).

An EOGRT study according to OECD TG 443 as specified in this decision is an information requirement for your registration, because Column 1 criteria at Annex IX, section 8.7.3 are met.

For the assessment of the information provided and the specifications of the study design see Appendix D.2.

3. Long-term toxicity testing on aquatic invertebrates

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

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

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

"*According to Regulation (EC) No.1907/2006, Annex IX, Section 9.1.5, Column 2, long-term toxicity testing on aquatic invertebrates may need to be conducted if the results of the chemical safety assessment indicate the need to investigate further the effects on aquatic organisms. The chemical safety assessment for this substance demonstrates that 1) the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC; and 2) the likelihood and severity of an event occurring due to the physicochemical properties of the substance is negligible, according to Annex 1, Section 6.4. Therefore, the criteria for adaptation are met. Specifically, all risk characterization ratios are under 1.0, based on PNECs derived from short-term toxicity studies on fish, aquatic invertebrates, and aquatic algae and plants, as demonstrated by the attached exposure assessments. Therefore, short-term toxicity data on fish, aquatic invertebrates and aquatic algae and plants are adequate to assess the environmental effects of pyridine, and long-term toxicity testing of aquatic invertebrates is not indicated*".

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to aquatic invertebrates under Column 1. It must be understood as a trigger for providing further information on aquatic invertebrates if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

In your comments to the initial draft decision you agree to perform the study with the Substance according to the OECD TG 211.

4. Long-term toxicity testing on fish

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

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:

"*According to Regulation (EC) No.1907/2006, Annex IX, Section 9.1.6, Column 2, long-term toxicity testing on fish may need to be conducted if the results of the chemical safety assessment indicate the need to investigate further the effects on aquatic organisms. The chemical safety assessment for this substance demonstrates that 1) the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC; and 2) the likelihood and severity of an event occurring due to the physicochemical properties of the substance is negligible, according to Annex 1, Section 6.4. Therefore, the criteria for adaptation are met. Specifically, all risk characterization ratios are under 1.0, based on PNECs derived from short-term toxicity studies on fish, aquatic invertebrates, and aquatic algae and plants, as demonstrated by the attached exposure assessments. Therefore, short-term toxicity data on fish, aquatic invertebrates and aquatic algae and plants are adequate to assess the environmental effects of pyridine, and long-term toxicity testing of fish is not indicated.*".

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.

Study design

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

In your comments to the initial draft decision you agree to perform the study with the Substance according to the OECD TG 210.

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

You have provided:
(i) Reproduction/Developmental Toxicity Screening Test (2008), according to OECD 421, with the Substance;
(ii) a data waiver (see waiver in section C.1).

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

For similar reasons as explained in section C.1, the waiver does not apply to this information requirement and the information provided is rejected.

Furthermore, you have not provided information on a second species. To be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

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

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request C.1 in this decision).

The study must be performed with oral[6] administration of the Substance.

2. Extended one-generation reproductive toxicity study

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided:
(i) Wistar rat/ F344 rat, 2 year combined repeated dose and carcinogenicity study, according to EPA OTS 798.3260 (Chronic Toxicity) (2000) with the Substance;
(ii) F344 rat, Combined Toxicity/Carcinogenicity study, similar to OECD TG 453 (2004), with the analogue substance 3-methylpyridine;
(iii) Mice, Combined Toxicity/Carcinogenicity study, similar to OECD TG 453 (2004) with the analogue substance 3-methylpyridine;
(iv) Reproduction/Developmental Toxicity Screening Test, according to OECD 421 (2008) with the Substance.

To be considered compliant and enable concluding if the Substance is a reproductive toxicant, the study has to meet the requirements of OECD TG 443 as specified in REACH. In the case of a grouping and read-across adaptation, the study must have adequate and reliable coverage of the key parameters of OECD TG 443 (Annex XI, Section 1.5).

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

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

Study (iv) provided in your dossier does not cover all relevant life stages required in OECD TG 443, as the extensive postnatal investigations of the fully exposed F1 generation up to the adulthood are not included. Furthermore, the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group as required OECD TG 443.

The studies (i)-(iii) provided in your dossier do not meet the requirement of OECD TG 443 or do not have adequate and reliable coverage of its key parameters as effects on mating, fertility, pregnancy, lactation and postnatal development of the fully exposed F1 generation up to the adulthood are not investigated.

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

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[13]

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Species and route selection

The study must be performed in rats with oral[7] administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and/or Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study.

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

Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[8].

[8] ECHA Guidance R.7a, Section R.7.6.

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[9].

B. Test material

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

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:

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

2. Information on the Test Material needed in the updated dossier

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

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

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

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

Appendix F: 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 01 October 2020.

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

In your comments on the initial draft decision, you requested the deadline to be extended to 42 months to allow sequential testing. However, you did not provide any proof for the extension need. Please note that the deadline originally proposed in the draft decision already takes sequential testing into account.

ECHA took into account your comments and did not amend the 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 G: List of references - ECHA Guidance[11] and other supporting documents

Evaluation of available information

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

QSARs, read-across and grouping

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

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

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[13]

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[14]

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.

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

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

[13] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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 H: 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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