~~Confidential~~

Helsinki, 10 February 2022

Addressees
Registrant(s) of JS-4-Vinylpyridine as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
24/04/2013

Registered substance subject to this decision ("the Substance")
Substance name: 4-vinylpyridine
EC number: 202-852-0
CAS number: 100-43-6

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 ***19 August 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. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. /OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

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

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

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

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

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

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

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

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test

method: EU C.20./OECD TG 211).

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

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

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

Information required depends on your tonnage band

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

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 following standard information requirement by applying a read-across approach in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.).

ECHA has considered the scientific and regulatory validity of your 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. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

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

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Section 7:

You read-across between the structurally similar substances, 2-Vinylpyridine, EC No. 202-879-8 (CAS No. 100-69-6) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: "[2-Vinylpyridine] *2VP and* [4-Vinylpyridine] *4VP are considered read-across analogues based on a common functional group; they are isomers. In aromatic ring systems, substituents in the 2 and 4 positions have similar chemical activities, based on the ability of the bonds to arrange in a conjugated fashion. This results in similar properties in physical and biological systems. 2VP and 4VP display characteristics of both pyridine and the vinyl group which comprises the constituent group. Their relative densities, water solubilities, partition coefficients (n-octanol: water), dissociation constants are almost identical (See Table 3). Neither substance is readily biodegradable by sludge or other organisms in screening tests. The partition coefficients (organic carbon) are similar.".*

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.

[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

1. Missing supporting information to compare properties of the substances

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose, "*it is important to provide supporting information to strengthen the rationale for the read-across*"[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 Substance and source substances.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

You have provided the following studies with the source substance 2-Vinylpyridine:

i. 1997, JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals with the source substance 2-Vinylpyridine with the following strains TA 1535, TA 1537, TA 98, TA 100, E. coli WP2 uvr A, which gave clear positive mutagenic responses in E. coli WP2 with metabolic activation conditions.
ii. 1984, a subchronic repeated dose toxicity study, similar to OECD TG 408 with the source substance 2-Vinylpyridine.
iii. 1984, similar to OECD TG 408 with the source substance 2-Vinylpyridine, EC 202-879-8;
iv. 1997, similar to OECD TG 407 with the source substance 2-Vinylpyridine, EC 202-879-8;
v. 1998, similar to TG 407 with the source substance 2-Vinylpyridine, EC 202-879-8.

You have also provided the following studies with the Substance:

vi. 1992, equivalent or similar to OECD 471 with the Substance with the following strains, TA 1535, TA 1537, TA 98, TA 100 which all gave negative results.
vii. 1980, equivalent or similar to OECD 471 with the Substance with the following strains, TA 1535, TA 1537, TA 98, TA 100 which all gave negative results.
viii. 1992, Williams Assey with the Substance, which gave negative results.
ix. 1992, non-guideline key study, "*A study of tobacco carcinogenesis XLVII. Bioassays of vinylpyridines for genotoxicity and for tumorigenicity in mice"* with the Substance.

As explained in the endpoint specific appendices, due to the deficiencies identified, the studies with the Substance (vi-ix) are not fulfilling the key parameters of the standard information requirements and therefore they can not be used to compare the properties between source substance and the Substance.

Therefore, the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance, but only on the source substance. Therefore, it is not possible to compare the properties of the target and of the source substance to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and of the source substance are likely to have similar properties. Therefore, you have not provided

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

sufficient supporting information to strengthen the rationale for the read-across.

2. *Adequacy and reliability of source study*

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

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

Deficiencies are addressed in the specific endpoint section below.

B. Conclusions on the read-across approach

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

2. Assessment of the (Q)SAR adaptation under Annex XI, Section 1.3.

You seek to adapt the following standard information requirements by applying (a) (Q)SAR approach(es) in accordance with Annex XI, Section 1.3:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

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

1. *Modelled endpoint not well defined*

Under ECHA Guidance R.6.1.3., a (Q)SAR model must fulfil the principles described in the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) to be considered scientifically valid. The first OECD principle requires the endpoint of a (Q)SAR model to be well defined. ECHA Guidance R.6.5.1.2 specifies that for a well-defined endpoint:

- the training set must be obtained from experimental data generated with homogeneous experimental protocols, and
- the effect modelled being predicted by the (Q)SAR must be the same as the effect measured by a defined test protocol relevant to the information requirement, which in this case includes fertility, reproductive performance and effects on offspring and developmental effects (as in OECD TG 421/422 and TG 414).

You specify that the effect that is modelled is reproductive toxicity in females, adult males and sperm toxicity). You have provided a (Q)SAR model [MC4PC ver.2.1 (2010)] which is based on data generated using the following methodologies:

The predictions are from three models (reproductive toxicity in females, adult males and sperm toxicity) using MC4PC modules for reprotoxity and for developmental toxicity predictions by Cat-SAR 2-Dimensional fragment-based SAR expert system Al Cunningham model (2008, version unknown) for Human Developmental Toxicity.

For reproductive and developmental toxicity you have not provided information establishing that the datasets of the models are based on homogenous protocols and it cannot be excluded that they were obtained from heterogeneous protocols. The dossier data does not specify if same or different species and experimental protocols were used.

Therefore, ECHA can not conclude whether the training set is obtained from experimental data generated with homogeneous experimental protocols.

None of the endpoints predicted by the (Q)SAR are demonstrated to be the same as the endpoint measured by the relevant test protocol. This is because the predictions are qualitative for all three endpoints predicted. The specific effects of the substance modelled for the two predicted endpoints are not known, neither is a NOAEL or any underlying data. The endpoint indicated in the QPRF mixes developmental and reproductive effects. It measures the effect in CASE units, which do not have a correspondence to measured experimental endpoints. The predicted endpoint is qualitative and it is not known what the conclusion is based on.

Therefore the endpoint of the model is not well defined and you have not established that the use of this model is a scientifically valid approach to meet this information requirement.

2. *Inadequate documentation of the model (QMRF)*

Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and ECHA Guidance R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

Detailed information on the experimental protocol and data quality for the data used to develop the model is missing. There is a list of fragments identified in the structure of the target for prediction, however the links to visualise the fragments do not work. Links provided to training and test set do not work, so the information there is unavailable. For example the endpoint described in QMRF is *Salmonella* mutagenicity instead of developmental toxicity. Training and test sets are not available.

In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

3. *Lack of or inadequate documentation of the prediction (QPRF)*

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You provided the following information about the prediction including the endpoints:

Information that refers to "CASE units" and a multitude of endpoints, mixing developmental and reproductive toxicity. As already addressed above, the prediction is qualitative and it is not demonstrated that the datasets the models are based on, are homogeneous. Therefore, it is not known from the documentation how the model predictions and the overall conclusions were derived.

The description of the domain is not transparent. Detailed information on how fragments were considered to derive domain definitions is not provided, even though there were links to fragments but they did not work.

Therefore, ECHA concludes that the documentation on the relationship between the modelled substance and the defined applicability domain is inadequate.

Furthermore, the "structural analogues" are mentioned in the QPFR containing the same structural fragments identified in the target, however close analogues of the target in the training set are not identified and considerations on the accuracy of their predictions is missing. Therefore, the documentation of close analogues, including considerations on how predicted and experimental data for analogues support the prediction is inadequate.

In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

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

1. In vitro gene mutation study in bacteria

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

You have provided a key study and a supporting study with the Substance in your dossier:

i. 1992, equivalent or similar to OECD 471 with the Substance with the following strains, TA 1535, TA 1537, TA 98, TA 100 which all gave negative results.
ii. 1980, equivalent or similar to OECD 471 with the Substance with the following strains, TA 1535, TA 1537, TA 98, TA 100 which all gave negative results.

Furthermore, you have provided an adaptation according to Annex XI, Section 1.5, and provided the following study with a source substance:

iii. 1997, JAPAN: Guidelines for Screening Mutagenicity Testing Of Chemicals with the analogue substance 2-Vinylpyridine with the following strains TA 1535, TA 1537, TA 98, TA 100, E. coli WP2 uvr A, which gave clear positive mutagenic responses in E. coli WP2 with metabolic activation conditions.

We have assessed this information and identified the following issues:

1. Studies not in line with the requirements in OECD 471

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471[5]. One of the key parameters of this test guideline includes:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The reported data for the studies you have provided (i. and ii.) did not include:

a) results for the appropriate 5 strains, that is in TA98/TA100/TA1535/TA1537 or TA97a or TA97/the required fifth strain, S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

Therefore, the provided studies do not fulfil the information requirement.

2. Grouping and read-across rejection

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

Therefore, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) should be performed using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

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

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:

i. a key study: 1992, Williams Assey with the Substance, which gave negative results.

In addition you have provided a waiver which references to the introduction of Annex VIII with the following justification: *"[…]In vitro studies, including a mutation assay in mammalian cells, are technically difficult due to the cytotoxicity of the substance. […]"*

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

1. OECD study other than in vitro cytogenicity/in vitro micronucleus

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 (Annex VIII, Section 8.4.2 of REACH and ECHA Guidance R.7, Table R.7.7-2).

The information provided (study i) 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 provided study does not fulfil the information requirement.

2. Waiver based on cytotoxicity

The study may be adapted if it is technically not possible under Section 2 of Annex XI of REACH, but there is no legal basis in REACH for the adaptation of in vitro information requirement due to are technically difficult due to the cytotoxicity of the substance.

You claim that *"In vitro studies, including a mutation assay in mammalian cells, are technically difficult due to the cytotoxicity of the substance."*

You argue that testing is difficult, not impossible. ECHA also observes that corrosive properties of substances in *in vitro* genotoxicity tests may lead to cytotoxicity, which is one criterion to determine the highest achievable test substance concentration. Therefore, you have not demonstrated that an *in vitro* test cannot be performed.

Therefore, your waiver is rejected and the information requirement is not fulfilled.

Therefore, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. In vitro gene mutation study in mammalian cells

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

i. Triggering of the study

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

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

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

ii. Assessment of information provided

You have provided an adaptation according to Annex VIII, Section 8.4.3, column 2, and provided the following study in your dossier:

i. 1992, non-guideline study, *"A study of tobacco carcinogenesis XLVII. Bioassays of vinylpyridines for genotoxicity and for tumorigenicity in mice"* with the Substance, a lung tumor induction assay*;*

In addition you have provided a waiver which references to the introduction of Annex VIII with the following justification: *"[…]In vitro studies, including a mutation assay in mammalian cells, are technically difficult due to the cytotoxicity of the substance. […]"*

We have assessed this information and identified the following issues:

1. OECD studies other than in vitro gene mutation study in mammalian cells

To be considered adequate, the study has to meet the requirements of OECD TG 474/489, and the key parameters of this test guideline include:

a) The study must include a minimum of three doses/groups of treated animals as well as a negative control group and a positive control group.
b) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia).
c) The proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 500 erythrocytes for bone marrow and 2000 erythrocytes for peripheral blood).
d) Where increases in DNA migration are observed, an examination of one or more indicators of cytotoxicity (e.g. inflammation, cell infiltration, apoptotic or necrotic changes) must be performed, as target tissue toxicity may result in increases in DNA migration.
e) At least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes.
f) At least 150 cells must be analysed for each sample (per tissue, per animal).
g) The proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes must be reported for each group of animals.
h) Data on the % tail DNA (or other measures, if chosen) and mean values per group should

be reported for the treated and control groups.
i) It is not appropriate to perform this test if there is evidence that the test substances, or a relevant metabolite, will not reach the target tissue.

ECHA acknowledges that you provided an *in vivo* non guideline study *(i)* performed with the Substance in order to follow up the concern for gene mutation and chromosomal aberration raised by the *in vitro* results. However, the reported data for the study do not include:
a) the appropriate number of doses
b) a maximum studied dose that is a MTD or induces toxicity
c) the analysis of the adequate number of cells
d) a negative control with a response inside the historical control range of the laboratory
e) a positive control group (or scoring control) that produced a statistically significant increase in the induced response compared with the concurrent negative control
f) data on the proportion of immature erythrocytes among total erythrocytes and the mean number of micronucleated immature erythrocytes for each group of animals
g) data on the mitotic index and the mean number of cells with aberrations per group for each group of animals
h) data on the mutation frequency for each tissue and for the treated and control groups
i) data on the % tail DNA (or other measures, if chosen) and mean values per group for the treated and control groups.

In addition, the information requirement is for informing on a concern for cytogenicity or gene mutation. However, the provided study (i) does not inform on either of these, instead this non-validated non-guideline study informs on tumour formation. Tumour formation does not inform on germ cell mutagenicity. The information provided does not cover key parameter(s) required by OECD TG 474 and 489. Therefore, the study does not fulfil the information requirement.

Therefore, the conditions set out in Annex IX, Section 8.4, column 2 are not met.

Therefore, the provided *in vivo* tests is not appropriate.

2. Waiver based on corrosivity

For the same reasons as explained in Section B.1 your waiver is rejected.

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

Consequently, you are required to provide information for this endpoint, if the information addressed under sections A.1 and B.1 provides a negative result.

Study design

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

3. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following source of information:

(i) 2011, a (Q)SAR Prediction Reporting Format for Pyridine, 4-ethenyl-.
(ii) 1984, a subchronic repeated dose toxicity study, similar to OECD TG 408 with the analogue substance 2-Vinylpyridine.

In addition, you have provided a waiver referring to paragraph three of the preamble of Annex VIII as pain and suffering is expected to occur in nearly all animals due to the corrosive property of the Substance.

In support of your waivers you have provided the following justification: *"the substance is corrosive and according to the introduction to Annex VII and IX, "in vivo testing with corrosive substances at concentration/doses causing corrosivity shall be avoided". No in vivo studies on 4-vinylpyridine are indicated."*

We have assessed this information and identified the following deficiencies:

1. *Weight of evidence*

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on reproductive/developmental toxicity.

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

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

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

You have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property investigated by the required study.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.1 at Annex VIII includes similar information that is produced by the OECD TG 421 or 422. At general level, it included information on 1) sexual function and fertility, 2) toxicity to offspring and examination of offspring parameter and 3) systemic toxicity.

a) *Sexual function and fertility*

Sexual function and fertility on both sexes must cover information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The repeated dose toxicity study (ii) provide relevant information on integrity of reproductive organs on both sexes. The study (i) provides information on structural alerts for reproductive toxicity and sperm toxicity.

The sources of information (i) and (ii) do not provide qualitative (ii) and quantitative (i and ii) information on functional fertility on males and females. The repeated dose toxicity study (ii) informs only about reproductive organs without mating of animals.

Therefore there is only partially information on sexual function and fertility.

However, the following deficiencies affect their reliability:

The source of information (i) has further deficiencies affecting its reliability as described under Appendix common to several request section 3. *Assessment of the (Q)SAR adaptation under Annex XI, Section 1.3.*

The source of information (ii) has further deficiencies affecting its reliability as described under Appendix common to several request section 1.These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

Further, functional fertility and histopathology of reproductive organs and tissues must be investigated in parental P0 animals as indicated in OECD TG 441/422 after at least 4 weeks for males and 9 weeks for females premating exposure duration.

The sources of information (i) and (ii) do not cover the full duration as defined in OECD TG 421/422.

In the absence of reliable information on sexual function and fertility with sufficient premating exposure duration for both parental P0 animals, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

b) Toxicity to offspring

Toxicity to offspring must cover information on deaths before, during or after birth, growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

The source of information (ii) investigates adult animals without producing offspring and therefore are lacking information on offspring. The source of information (i) does not provide relevant information to deaths before, during or after birth, on growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

Therefore, only source of information (i) provide relevant information and only partially. It is however, not reliable as mentioned above.

c) Systemic toxicity

Information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

Information on general organ toxicity, haematology and clinical chemistry is available from the provided study (ii) for parental animals but not from source (i).

Taken together, the sources of information as indicated above, provide relevant information on systemic toxicity but only partially relevant information on sexual function and fertility and no relevant information on toxicity to offspring.The reliability of the information provided is further significantly affected.

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 421/422 study with a design described in this decision. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2. *Waiver based on corrosivity*

According to paragraph 3 of the preamble of Annex VIII and OECD TG 421/422, testing at doses causing corrosivity must be avoided. The test guideline provides rules accommodating irritative and corrosive properties by e.g. adjusting the volume of vehicle.

You claim that the test guideline requires doses demonstrating toxicity in the target organ and this would be at a dose causing corrosivity. An existing study (1997, similar to OECD TG 407 with the analogue substance 2-vinylpyridine) shows effects of systemic toxicity at doses with test substance, tested up to 200 mg/kg bw/d, without mortality or excessive suffering of test animals.

Paragraph 3 of the Preamble of Annex VIII is not a legal basis for adaptation, but sets a consideration to address when carrying out testing. Further, you misquote the OECD TG by not taking into account that there are ways to test corrosive substances provided by the OECD TG, such as modulating the vehicle volume. Furthermore, the pH can be adjusted with buffers towards more physiological values. In any case, you have not substantiated your claim that the dose that would result in toxicity in the target organ is actually corrosive. The existing study in an analogue substance with similarly corrosive properties (1997, similar to TG 407 with 2-vinylpyridine), suggests the contrary.

Therefore, your waiver is rejected and the information requirement is not fulfilled.

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

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[6] administration of the Substance. A corrosive property of the test substance may be counteracted by increasing the volume of vehicle (para 32 in TG 422), and/or buffering to a more physiological pH.

In your comments on the initial draft decision you agree to perform a pre-natal developmental toxicity study instead of the screening study.

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

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

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

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

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

In support of your adaptation you have provided a key study and two supporting studies.
(i) 1984, similar to OECD TG 408 with the analogue substance 2-Vinylpyridine, EC 202-879-8;
(ii) 1997, similar to OECD TG 407 with the analogue substance 2-Vinylpyridine, EC 202-879-8;
(iii) 1998, similar to TG 407 with the analogue substance 2-Vinylpyridine, EC 202-879-8.

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

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 methods, in this case OECD TG 408. The following key parameter(s) of this test guideline include, among others:

- At least 10 female and 10 male animals should be used at each dose level (including control group)
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

The studies (ii) and (iii) you have provided were conducted with less than 10 animals per sex per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408. Furthermore, the above mentioned studies (ii) and (iii) you have provided do not have the required exposure duration of 90 days as required in OECD TG 408, because you indicated an exposure duration of 28 (ii) and 14 (iii) days, respectively.

Therefore, the information requirement is not fulfilled.

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

Information on the design of the study to be performed (route/ species/ strain)
Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the substance is corrosive and is expected to lead to excessive toxicity at the local site of contact via the inhalation route. This would be dose-limiting and contradicting the purpose of the request study to investigate systemic toxicity.

Therefore, the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance. A corrosive property of the test substance may be counteracted by increasing the volume of vehicle (para 20 in TG 408), and/or buffering to a more physiological pH.

2. Pre-natal developmental toxicity study in one species

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

You have provided a QSAR adaptation using the following information:

(i) 2012, Qualitative SAR prediction, Cat-SAR Human Developmental Toxicity-4-Vinylpyridine

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

A. Assessment of your (Q)SAR adaptation

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

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

Information on study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[7] administration of the Substance. A corrosive property of the test substance may be counteracted by increasing the volume of vehicle and/or buffering to a more physiological pH.

The study shall be performed with oral[8] administration of the Substance.

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

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 the following information, which, ECHA understands, is intended to refer to Section 9.1.5, not Section 9.1.6:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1.5, Column 2. In support of your adaptation, you provided the following justification: "*According to Regulation (EC) No. 1907/2006, Annex IX, Column 2, 9.1.6, long term toxicity testing shall be proposed if the chemical safety assessment according to Annex 1 indicates the need to investigate further the effects on aquatic organisms. Additional testing in invertebrates is not indicated based on the acute toxicity of 4VP. 4VP is classified as Chronic Category 2 and its release into the environment will be minimized.*"

We have assessed this information and identified the following issue:

Annex IX, Section 9.1.5, 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.

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

4. Long-term toxicity testing on fish

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

You have provided the following information:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1.6, Column 2. In support of your adaptation, you provided the following justification: *"According to Regulation (EC) No. 1907/2006, Annex IX, Column 2 , 9.1.6, long term toxicity testing shall be proposed if the chemical safety assessment according to Annex 1 indicates the need to investigate further the effects on aquatic organisms. Additional testing in vertebrates is not indicated based on the acute toxicity of 4VP. 4VP is classified as Chronic Category 2 and its release into the environment will be minimized."*

We have assessed this information and identified the following issue:

Annex IX, Section 9.1.6, 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 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.

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.).

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

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[9].

B. Test material

1. Selection of the Test material(s)

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

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 E: Procedure

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

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

The compliance check was initiated on 1 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 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 F: List of references - ECHA Guidance11 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]

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

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

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

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

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

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

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

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