~~Confidential~~

Helsinki, 07 December 2021

Addressees
Registrant(s) of JS_CAS1129-42-6 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
24/05/2013

Registered substance subject to this decision ("the Substance")
Substance name: 6-methyl-2-oxoperhydropyrimidin-4-ylurea
EC number: 214-447-6
CAS number: 1129-42-6

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 ***13 March 2024***.

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

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

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

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

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

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

2. 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

3. 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. 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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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 A: Appendix on Reasons common to several requests

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

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) 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.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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

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 and ecotoxicological properties

You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substance, **N,N"-(2-methylpropane-1,1-diyl) diurea** (CAS No. 6104-30-9) as source substance and the Substance as target substance.

In the justification document you claim that "*On the basis of all evaluated data, the similarity of the analogue and source substances* […] *is justified on the basis of the physico-chemical properties, toxicological profiles and supported by various QSAR methods*."

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

ECHA notes the following shortcomings with regards to predictions of toxicological and ecotoxicological properties.

Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. 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 (read-across approach).

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 substances[4]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties.

You have provided information on the structures of target and sources substances. More notably, you claim that "*The chemical structures and physico-chemical properties of both substances are very similar*."

However, there are structural differences between source and target substances. According to your read-across justification document "*the structural difference is manifested in the presence of a lactam (i.e. cyclic amide) group in the target and alkane, branched with tertiary carbon, in the source molecule.*"

You have not explained why these differences would not imply that the (eco)toxicological effects differ. Therefore, you have not demonstrated that it is possible to derive a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural differences between the target and source substance.

Supporting information

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*"[5]. 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).

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).

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

You have provided an in vivo Mammalian Erythrocyte Micronucleus Test, a screening study according to OECD Guideline 422, a study similar to OECD TG 416 and a study according to OECD Guideline 414 specified below on the source substance, while you did not provide studies on these toxic effects of the Substance.

The data set reported in the technical dossier does not include relevant, reliable and adequate (eco)toxicological information for the Substance and of the source substance(s) to support your read-across hypothesis.

In the absence of such information, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

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:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- 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 in this respect are addressed under the corresponding Appendix.

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.

Appendix B: 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 the standard information requirement according to Annex XI, Section 1.2. of REACH (Weight of evidence).

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

i. A study with the Substance, according to EEC Directive 93/32/EEC ([redacted] 2004)[6].
ii. A study with the read-across substance, N,N"-(2-methylpropane-1,1-diyl) diurea (CAS No. 6104-30-9), according to Directive 84/449/EEC, C.2 ([redacted] 1988)[7].

We have assessed this information and identified the following issues:

Annex XI, Section 1.2 states that there may be sufficient weight of evidence (WoE) 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 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, 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/hazardous) 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.

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 9.1.1 at Annex VII includes similar information that is produced by the OECD TG 202.

OECD TG 202 requires the study to investigate the following key investigation:

[redacted]

- the concentration of the test material leading to the immobilisation of 50% of the daphnids at the end of the test is estimated.

Coverage of key investigations

The two sources of information i and ii may provide information on the immobilisation of the daphnids.

Reliability of the experimental studies i. and ii. listed above

However, the reliability of these sources of information is significantly affected by the following deficiencies:

Read-across not accepted for study ii

Information from a source substance can be used as part of weight of evidence adaptation if the read-across is accepted. However, the information from (ii) with source substance N,N"-(2-methylpropane-1,1-diyl) diurea (CAS No. 6104-30-9) has significant deficiencies as explained in the Appendix on Reasons common to several requests. Therefore it cannot be used as part of the weight of evidence adaptation.

No analytical monitoring of the test concentrations was conducted for studies i and ii

The specifications of OECD TG 202 indicate that the concentrations of the test material should be measured at least at the highest and lowest test concentration, at the beginning and end of the test.

However, for both studies i. and ii, no analytical monitoring of the test concentrations was conducted.

This is a critical methodological deficiency because the actual concentrations to which the test organisms have been exposed are unknown for both studies.

In your dossier, a water solubility of 5.065 g/L at 20 °C and pH = 8.57-8.69 is reported for the Substance, and water solubility values ranging from 0.3 to 3 g/L for the read-across substance. However, according to the literature (Dittmar et al. 2009)[8], the water solubility of both the Substance and of the read-across substance strongly depends on the temperature and pH. No information on the test temperature and pH is reported for study i.

For study ii, a temperature of 19 - 21°C and pH 7.84-8.08 are reported, but it is also mentioned that undissolved test substance was visible in the stock solution and in the test vessels over the whole test period.

Therefore there are indications that the test substance was only partially dissolved in study ii and it cannot be ruled out that the test substance was only partially dissolved in study i.

Therefore the results from both studies are considered not reliable.

As a conclusion, sources of information as indicated above, provide information on the immobilisation of daphnids, but the information provided is not reliable.

[8] Dittmar, Heinrich; Drach, Manfred; Vosskamp, Ralf; Trenkel, Martin E.; Gutser, Reinhold; Steffens, Günter (2009). "Fertilizers, 2. Types". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH

Based on the assessment above, 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 property foreseen to be investigated in an OECD TG 202 study.

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

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 a read-across adaptation under Annex XI, Section 1.5 using a study performed on species *Desmodesmus subspicatus*, according to test guideline DIN 38412 Part 9, with read-across substance N, N"-(2-Methylpropyldiene)Bis; CAS No: 6104-30-9.

We have assessed this information and identified the following issues:

Your read-across adaptation is not accepted as explained above in the Appendix on Reasons common to several requests.

In addition, we identified the following issues with this study.

As explained in the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 201, which includes that the concentrations of the test material should be 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}.

However, for the study provided in your registration dossier, no analytical monitoring of the test concentrations was conducted.

Based on the above, there is no reliable coverage of the key parameters of the OECD TG 201. More, specifically water solubility values ranging from 0.3 to 3 g/L are reported for the read-across substance (Dittmar et al. 2009). Its water solubility depends on the temperature and pH. For the study provided, a test temperature of 23°C is reported. In the short-term studies on *Daphnia* (Appendix A.1) with this read-across substance, undissolved test material was observed for equivalent test concentrations and test temperature.

Therefore it cannot be ruled out that the test substance was only partially dissolved in the study provided for this information requirement. Consequently, the actual concentrations to which the test organisms have been exposed are unknown for this study.

On this basis, the information requirement is not fulfilled.

Appendix C: 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.).

In your registration dossier, you have provided a read-across adaptation under Annex XI, Section 1.5 for adapting this information requirement under Column 2 of Section 8.4.2, using a key study in your dossier:

- In vivo Mammalian Erythrocyte Micronucleus Test, OECD Guideline 474, with an analogue substance **N,N"-(2-methylpropane-1,1-diyl) diurea,** EC No. 228-055-8, (CAS No. 6104-30-9) performed in 1999, reliability 2, according to GLP

In your comments to the initial draft decision you provided profiling results with the OECD QSAR Toolbox v.4.4. You acknowledge that there are structural differences between the source and target substances. You claim that the "QSAR toolbox profiling can demonstrate how the presence of the different functional groups in the target and source substance will not influence the genetic toxicity profiles, in relation to neither gene mutation nor cytogenicity" and "demonstrates sameness with respect to genetic toxicity profiles for the target and source substances".

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

Your read-across adaptation is not accepted. As explained in the Appendix on Reasons common to several requests, this is primarily because of the lack of consideration of structural differences in your read-across hypothesis but also for the lack of supporting information.

In your comments to the initial draft decision you acknowledged that there are structural differences between the source and target substances. However, you claim that the "*QSAR toolbox profiling can demonstrate how the presence of the different functional groups in the target and source substance will not influence the genetic toxicity profiles, in relation to neither gene mutation nor cytogenicity*" and "*demonstrates sameness with respect to genetic toxicity profiles for the target and source substances*".

Regarding these statements in your comments, ECHA points out that, while the similarity in presence or absence of some structural alerts may suggest that the differences do not influence the reactivity of the substance e.g. on DNA, this information does not confirm, on its own, that the Substance and the source substance have similar toxicological properties such as genotoxicity.

ECHA further notes that Toolbox profilers are models developed for the purpose of identifying analogues and not to make predictions (as indicated on the official QSAR Toolbox website https://qsartoolbox.org/features/profiling/).

We also note that data on gene mutations cannot be used as bridging information for cytotoxicity, because the relevant tests concern two different toxic endpoints.

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

Study design

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

suitable.

2. Screening study 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, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

You have provided a read-across adaptation under Annex XI, Section 1.5. using two key studies for this endpoint in your dossier:

i) A screening study according to OECD Guideline 422 with an analogue substance, **N,N"-(2-methylpropane-1,1-diyl) diurea,** EC No 228-055-8, (CAS No. 6104-30-9), reliability 2, according to GLP, made in 2003,

ii) A study similar to OECD TG 416, with an analogue substance **N,N"-(2-methylpropane-1,1-diyl) diurea** EC No. 228-055-8, (CAS No. 6104-30-9), reliability 2, according to GLP, made in 2003,

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

Your read-across adaptation is not accepted as explained above in Appendix on Reasons common to several requests.

In addition, we identified the following issues related to the studies you provided.

As explained in the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this caseEU B.63/OECD TG 421 or EU B.64/OECD TG 422, which includes for example

- Testing of at least three dose levels and a concurrent control),
- Examination of offspring parameters such as anogenital distance/number of nipples/areolae in male pups
- Clinical biochemistry
- Weights and histopathology of organs and tissues

The study ii) you have provided was conducted with:

- two dose levels, no investigations for anogenital distance, number of nipples and areolae in male pups, no clinical biochemistry determinations, no the weights and histopathology of organs and tissues. .

Therefore, there is no reliable coverage of the corresponding key parameters.

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[9] administration of the Substance. [

3. 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.).

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

You have provided a read-across adaptation under Annex XI, Section 1.5 using a study performed on species *Oncorhynchus mykiss*, according to test guideline OECD 203, with read-across substance N, N"-(2-Methylpropyldiene)Bis; CAS No: 6104-30-9.

We have assessed this information and identified the following issues:

Your read-across adaptation is not accepted as explained above in the Appendix on Reasons common to several requests.

In addition, we identified the following issues with this study.

As explained in the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 203, which includes that the analytical measurement of the test concentrations must be conducted.

However, for the study provided in your registration dossier, no analytical monitoring of the test concentrations was conducted.

Based on the above, the key parameters of the corresponding TG are not reliably covered. More, specifically water solubility values ranging from 0.3 to 3 g/L are reported for the read-across substance (Dittmar et al. 2009). Its water solubility depends on the temperature and pH. For the study provided, a test temperature of 12°C is reported. Your dossier indicates that undissolved test substance was visible on the water surface and on the bottom of the aquarium.

Therefore it cannot be ruled out that the test substance was only partially dissolved in the study provided for this information requirement. Consequently, the actual concentrations to which the test organisms have been exposed are unknown for this study.

On this basis, the information requirement is not fulfilled.

Appendix D: 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 provided a read-across adaptation under Annex XI, Section 1.5 using two key studies for this endpoint in your dossier:

i) A screening study according to OECD Guideline 422 with an analogue substance, **N,N"-(2-methylpropane-1,1-diyl) diurea,** EC No 228-055-8, (CAS No. 6104-30-9), reliability 2, according to GLP, made in 2003,

ii) A study similar to OECD TG 416, with an analogue substance **N,N"-(2-methylpropane-1,1-diyl) diurea,** EC No 228-055-8, (CAS No. 6104-30-9), reliability 2, according to GLP, made in 2003.

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

Your read-across adaptation is not accepted as explained above in Appendix on Reasons common to several requests.

In addition, we identified the following issues related to the studies you provided.

As explained in the Appendix on Reasons common to several requests, a study must have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this caseOECD TG 408, which include, among others

- testing of at least three dose levels and a concurrent control,
- recording hematology, clinical biochemistry, and histopathology, and
- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study, and
- 10 animals per sex per group

The study ii) you have provided was conducted with less than three dose levels.

The studies i) and ii), have the following key parameters missing: histopathology, hematology, clinical chemistry

Study i) had the exposure duration of the screening test is approximately 63 days (for females) and 28 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using 5 animals per sex per group.

The studies i) and ii) do not provide reliable coverage of the key parameters of the OECD TG 408, and you did not justify why some deviations from the OECD TG 408 can be considered acceptable.

Therefore, there is no reliable coverage of the corresponding key parameters.

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 a liquid of very low vapour pressure (below 0.35 Pa at 20°C) and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

2. Pre-natal developmental toxicity study

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 read-across adaptation under Annex XI, Section 1.5 using:

- A study according to OECD Guideline 414, with an analogue substance **N,N"-(2-methylpropane-1,1-diyl) diurea,** EC No 228-055-8, (CAS No. 6104-30-9), reliability 2, according to GLP, made in 1993

We have assessed this information and identified the following issue:

Your read-across adaptation is not accepted as explained above in Appendix on Reasons common to several requests.

Based on the above, the information you provided does 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[10] administration of the Substance.

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:

"*According to Annex IX of Regulation (EC) No 1907/2006 long-term toxicity tests on aquatic invertebrates do not need to be conducted if the chemical safety assessment of a substance indicates the no need for a further investigation of the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 6-methyl-2-oxoperhydropyrimidin-4-yl urea indicates no need to either classify the as dangerous to the environment, nor is 6-methyl-2-oxoperhydropyrimidin-4-yl urea a PBT or vPvB substance. Thus no long-term toxicity tests on aquatic invertebrates are provided"*.

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 and the information requirement is not fulfilled.

4. Long-term toxicity testing on fish

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

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:

"*According to Annex IX of Regulation (EC) No 1907/2006 long-term toxicity tests on fish do not need to be conducted if the chemical safety assessment of a substance indicates the no need for a further investigation of the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of 6-methyl-2-oxoperhydropyrimidin-4-yl urea indicates no need to either classify the as dangerous to the environment, nor is 6-methyl-2-oxoperhydropyrimidin-4-yl urea a PBT or vPvB substance. Thus no long-term toxicity tests on fish are provided"*.

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 and the information requirement is not fulfilled.

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[11].

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[12].

[11] https://echa.europa.eu/practical-guides
[12] 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 1 December 2020.

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

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

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[13] 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)[14]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[15]

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[16]

[13] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[14] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[15] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[16] 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 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]

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.