EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 11 February 2021

Addressees
Registrant(s) of JS_PigmentYellow65 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
22 April 2015

Registered substance subject to this decision ("the Substance")
Substance name: 2-[(4-methoxy-2-nitrophenyl)azo]-N-(2-methoxyphenyl)-3-oxobutyramide
EC number: 229-419-9
CAS number: 6528-34-3

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 in A.1 and A.2 below by ***16 November 2021*** and all other information listed below by ***19 May 2023***.

We note that the information submitted jointly in section 4.1 of the IUCLID dossier states that *"it is conceivable that the substance subject to registration could be considered as falling within the boundaries of the nanomaterial definition"*. This indicates that the Substance can be possibly manufactured or imported in the European Union in nanoforms by any addressee of the present decision. However, the REACH Regulation (as amended by Regulation Commission Regulation (EU) 2018/1881) sets out explicit information requirements for nanoforms of substances. Manufacturers and importers of nanoforms must have fulfilled these specific information requirements by 1st January 2020. As far as the registration dossier currently submitted on the Substance does not cover any nanoform, the incompliances identified in the present decision relate only to information required on non-nanoforms.

Based on the above, the information requested in this decision must be generated using exclusively non-nanoforms of the Substance.

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. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105)

2. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; test method: EU A.8 or OECD TG 117 or OECD TG 123)

3. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., Column 2)

4. 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. If negative results are obtained in test performed for the information requirement of 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. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)

4. 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

5. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., Column 2)

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 413) by inhalation 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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

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

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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 Christel Schilliger-Musset, 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. for the category of 'Monoazo Yellow Pigments'

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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

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

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

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you have formed a group (category) of 'Monoazo Yellow Pigments'. You have provided read-across justification in Section 1, Part B of your CSR.

For the purpose of this decision, the following abbreviations are used for the group members:
1) **PY1** C.I. PIGMENT YELLOW 1 (EC 219-730-8, CAS RN 2512-29-0);
2) **PY3** C.I. PIGMENT YELLOW 3 (EC 229-355-1, (CAS RN 6486-23-3);
3) **PY65** C.I. PIGMENT YELLOW 65 (EC 229-419-9, CAS RN 6528-34-3);
4) **PY73** C.I. PIGMENT YELLOW 73 (EC 236-852-7, CAS RN 13515-40-7);
5) **PY74** C.I. PIGMENT YELLOW 74 (EC 228-768-4, CAS RN 6358-31-2);
6) **PY97** C.I. PIGMENT YELLOW 97 (EC 235-427-3, CAS RN 12225-18-2) and
7) **PY111** C.I. PIGMENT YELLOW 111 (EC 240-131-2, CAS RN 15993-42-7).

You provide the following reasoning for the grouping the substances: all members have similar chemical structure and similar physical-chemical properties.

You define the applicability domain of the category as follows: The pigments grouped in this category are structurally similar and contain a [redacted]

[redacted]. Substituents may vary between [redacted] in case of PY 97.

ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

ii. Assessment of the grouping

ECHA notes the following shortcomings with regards to your grouping approach:

Applicability domain of the category

A category (grouping) hypothesis must address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint*" (ECHA Guidance R.6.2.4.1). Particularly, "*the applicability domain of a (sub)category would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members*" (ECHA Guidance R.6.2.1.2). Therefore, to reliably predict properties within a category the applicability domain must be described including the borders of the category, for which chemicals the category does not hold and a justification for the inclusion and/or exclusion rules.

You describe the applicability domain of the substances covered by the grouping as: substances containing a substituted phenyl moiety, an azo moiety, and an oxobutyramide moiety. You indicate that the substituents may vary but without defining the borders of the category.

Therefore, you have not provided unambiguous inclusion/exclusion criteria for substituents that can be linked to the core chemical structures of the selected group members nor a justification for the boundaries of the category.

B. Prediction for (eco)toxicological properties

You have provided the following reasoning for the prediction of (eco)toxicological properties:

- *Structural similarity:* the category members are structurally similar and only differ in the identity of the substituents attached to the core chemical groups;
- *Similar physico-chemical properties:* the category members are solids which decompose at high temperatures, their solubility in water and n-octanol is very limited;
- *Similar low bioavailability:* the category members have low bioavailability to both macro and micro-organisms and you consider this hypothesis to be supported by the lack of effects seen in acute oral or dermal studies, skin or eye irritation studies, skin sensitizing studies, toxicity after repeated dose toxicity studies and mutagenic studies. You also claimed a lack of toxicity in aquatic and terrestrial organisms as well as on bacteria.

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 substances.

i. Toxicological endpoints

You intend to predict the properties of the Substance from information obtained from the following category members:

In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.):
- PY1, an OECD TG 473 GLP study, [redacted] (2012)
- PY74, an OECD TG 487 GLP study, [redacted] (2009)

In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.):
- PY1, an OECD TG 476 GLP study, [redacted] (2012)
- PY74, non-guideline, Cameron (1987)

Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.):
- PY1, an OECD 422 GLP study, [redacted] (2012)
- PY1, a study similar to OECD TG 407 non GLP study, [redacted] (1979)
- PY1, non-guideline, [redacted] (1970)
- PY3, non-guideline, [redacted] (1958)
- PY3, non-guideline, [redacted] (1971)
- PY97, non-guideline, [redacted] (1960)

Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.):
- PY74, an OECD TG 408 GLP study, [redacted] (2009)

Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- PY1, an OECD 422 GLP study, [redacted] (2012).

ii. Aquatic toxicity endpoints

You intend to predict the properties of the Substance from information obtained from the following category members:
Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- PY1, an OECD TG 201 study (2012, GLP, [redacted]
- PY65, an OECD TG 201 study (2012, GLP, [redacted])
- PY74, an OECD TG 201 study (2009, GLP, [redacted])

Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- PY1, an OECD TG 211 study (2012, GLP, [redacted]
- PY74, an OECD TG 211 study (1999, GLP, [redacted]

iii. Assessment of your read-across justification

ECHA notes the following shortcomings that apply to both the predictions of toxicological and aquatic toxicity properties:

A. Missing 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*" (ECHA Guidance R.6.2.2.1.f). 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 other category members.

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

this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substances is necessary to confirm that both substances cause the same type of effects.

In this context, supporting information must include relevant bridging studies to compare the properties of the category members. Furthermore, your read-across hypothesis is based on similar (low) bioavailability of the group members, therefore supporting information must be provided to demonstrate your claim, such as:

- physico-chemical indicators suggesting a hindered uptake due to large molecular size (e.g. Dmax > 17.4 Å and MW > 1100 or MML > 4.3 nm);
- toxicokinetics studies to support the absence of uptake for all the category members;
- experimental evidence supporting the absence of mammalian toxicity following repeated exposure and of chronic ecotoxicity for all the category members.

Information from your dossier to support low bioavailability

In your read-across justification document, you have not provided information that would support a hindered uptake due to large molecular size. Then, on toxicokinetics, the only information provided is a non-guideline, non-GLP study with the category member PY74 ([redacted] 1984) which investigated absorption, distribution and excretion after a single oral dosing. Detectable amounts were seen only in those tissues directly in contact with the compound, which were attributed to mechanical adherence to the tissues rather than to absorption.

Your registration dossier also provides a sub-chronic repeated dose toxicity study (90-d) via the oral route with PY74. Significantly elevated liver weights of the high dosed females and small but significant haematological changes were noted which are indicative of systemic exposure. In an OECD TG 422 study with PY1 some effects indicative of absorption of the test substance were also observed, namely changes is the motility of sperms at the higher doses.

First, we note that you have not demonstrated that the structural properties of the category members may lead to hindered uptake. Then, we note that the toxicokinetic study by [redacted] (1984) on PY74 provides little support to conclude on the lack of bioavailability of this analogue as the study suffers from major study deficiencies (e.g., only one dose used instead of minimum two, only three animals used when at least four animals of the appropriate sex, no information provided on the validity of the analytical method). We also note that you have provided no toxicokinetic information on any other category members.

Finally, the information provided in a sub-chronic repeated dose toxicity study (90-d) via the oral route with PY74 and in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test with PY1 do not support the lack of bioavailability of these category members as effects were observed. We further note, that as further explained in B.3 and C.1, your registration dossier does not include any other adequate short-term (28-d) studies, screening studies (OECD TG 421/422) or sub-chronic (90-d) repeated dose toxicity studies for the other category members.

On the basis of the above, your justification does not include adequate supporting information to demonstrate that all category members have low bioavailability.

Bridging information on the category members

For toxicological endpoints, you have provided bridging information for the Substance and the category members for *in vitro* gene mutation in bacteria (OECD TG 471). However, for the other higher tier toxicological endpoints you have not provided adequate and reliable bridging information for all category members.

For ecotoxicological endpoints, you have provided information on short-term toxicity on aquatic invertebrates and on fish for the Substance and/or some category members. For growth inhibition to algae, you have provided information on the Substance and two category members (i.e. PY1 and PY74). Your registration dossier also includes two studies on long-term toxicity to aquatic invertebrates for the category members PY1 and PY74.

First, as further explained below under the corresponding Appendix, there are major deficiencies with a number of the studies provided on the Substance and the category members.

Furthermore, for toxicological endpoints, your dossier does not provide appropriate bridging studies (such as a screening study (OECD TG 421 or 422) or a short-term repeated dose toxicity study (OECD TG 412 or OECD TG 413)) to compare the properties of the category members with regard to repeated dose and reproductive/developmental toxicity.

Finally, for ecotoxicological endpoints, short-term studies do not give a true measure of toxicity for poorly water substances, as further explained under Appendix A.3 and B.5. Consequently these cannot be regarded as reliable bridging information. Then, as explained under Appendix A.3, the study on growth inhibition to algae suffers from methodological deficiencies and therefore provides limited support to conclude that the Substance and the two selected category members have similar ecotoxicological properties.

On the basis of the above, your justification does not include adequate bridging studies to demonstrate that all category members may be expected to show similar (eco)toxicological properties.

In the absence of such information, you have not established that the category members are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

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

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

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

1. Water solubility

Water solubility is an information requirement under Annex VII to REACH (Section 7.7.).

You have provided the following information:

- Water solubility study according to the ETAD shake flask method with the Substance ([redacted] 2010).

We have assessed this information and identified the following issue:

A. To fulfil the information requirement, a study must comply with the OECD TG 105 or the EU Method A.6 (Article 13(3) of REACH). Therefore, the following specifications must be met:
   - the shake-flask method is applicable to test material with a water solubility ≥ 10 mg/L;
   - solids are pulverized before testing;
   - the test is conducted with a loading of about five times the quantity required to saturate a given volume of water;
   - three flasks are included which are shaken/stirred for 24, 48 and 72 hours, respectively;
   - after shaking/stirring, each flask is equilibrated for 24 hours at 20°C;
   - the results are considered acceptable, if the results of the flasks shaken for 48 and 72 hours differ by ≤ 15%. If the results shows a tendency of higher solubility with longer shaking/stirring period, the test is repeated with longer equilibration times;
   - a reliable analytical method is available.

   Your registration dossier provides a study showing the following:
   - the water solubility was determined to be 1.9 µg/L, hence below 10 mg/L;
   - the fact that the test material was pulverized or not before testing is not reported;
   - about 5 mg of the test sample were suspended in 30 mL bidistilled water in a sample flask;
   - triplicate determination of test samples were shaken for two hours at 30°C (+/- 2°C) and then at ambient temperature (c.a.24-25°C) for 70 hours;
   - the test material concentration was determined UV-VIS. The calibration curve was produced using chloroform as solvent, while the substance is quantified in water. The measurement were made with lambdamax (438 nm) and absorbance at 526 nm measured in chloroform.

   Based on the above, the shake-flask method described in OECD TG 105 is not applicable to the Substance as its solubility is estimated to be well below 10 mg/L. Furthermore, the test design, the loading rate and the sample preparation method are not compliant with the guideline requirements. Finally, the analytical method used in this study did not allow providing a reliable estimate of dissolved concentration. Indeed, there is inherent uncertainty related to the measurement of low absorbance values and to the fact that the calibration curve and test samples use different solvents (i.e. chloroform versus water, which have different λmax).

   Therefore, the requirements of OECD TG 105 are not met.

On the basis of the above, the information requirement is not fulfilled.

Study design

Considering the properties of the Substance (solubility < 10 mg/L), the column elution described in EU A.6/OECD TG 105 is the most appropriate method to fulfil the information requirement for the Substance.

2. Partition coefficient n-octanol/water

Partition coefficient in n-octanol/water is an information requirement under Annex VII to REACH (Section 7.8.).

You have provided the following information:

- a study based on the ETAD method with the Substance ([redacted] 2012).

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study must comply with the OECD TG 107 or OECD TG 117 or OECD TG 123 or the EU Method A.8 (Article 13(3) of REACH). These test guidelines describe three methods (the shake flask method, the HPLC method and the slow-stirring method) for conducting the determining the partition coefficient between water and n-octanol (Log Kow). The EU Method A.8 specifies that the method selection must be based on the properties of the substance and on a preliminary determination of Log Kow using the individual solubilities of the test material in water and n-octanol. This preliminary estimate is considered sufficient only if none of the recommended method are technically feasible due to specific substance properties (*e.g.* surface active substances).

   Your robust study summary reports that the study was conducted according to the ETAD method where log Kow is determined using the individual solubilities of the test material in water and n-octanol. You have not provided any justification as to why none of the methods listed above are technically feasible.

B. To provide an acceptable determination of the partition coefficient using individual solubilities in water and n-octanol, the calculation must be based on reliable individual solubilities estimates.

   You used the information discussed under Section A.1 as the water solubility estimated used in the calculation. You report that the n-octanol solubility estimate was determined using a similar method.

   As explained under Section A.1, the information provided in your registration does not fulfil the information requirement. Furthermore, as a similar approach was used to determine n-octanol solubility, similar issues identified under Section A.1 also apply to the determination of n-octanol solubility. Hence, the log Kow value reported in your registration dossier is not reliable.

   Therefore, this study does not meet the information requirement.

On the basis of the above, the information requirement is not fulfilled.
Study design

Considering the properties of the Substance (sparingly soluble particles), the Partition Coefficient (n-octanol/water), HPLC Method (test method: OECD TG 117) or alternatively the

Partition Coefficient (1-Octanol/Water): Slow-Stirring Method (test method: OECD TG 123) are the most appropriate method to fulfil the information requirement for the Substance.

3. Growth inhibition study aquatic plants

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

You have provided the following information:

- a study according to OECD TG 201 on the Substance (Noack, 2012); study i.
- an adaptation under Annex XI, Section 1.5. In support of your adaptation, you provided the following studies:
  - a study according to OECD TG 201 on PY1 ([redacted] 2012); study ii.
  - a study according to OECD TG 201 on PY74 ([redacted] 2009); study iii.

We have assessed this information and identified the following issues:

A. To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH) or, in the case of read-across, have adequate and reliable coverage of the key parameters of that test guideline (Annex XI, Section 1.5). Therefore, the following specifications must be met:

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
- the concentrations of the test material are measured at least at the beginning and end of the test:
  1) at the highest, and
  2) at the lowest test concentration, and
  3) at a concentration around the expected EC_{50}.

Additional requirements applicable to difficult to test substances

- if the test material is poorly water soluble, the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions is determined;
- if losses of the test material are expected within the timeframe of the test, a preliminary stability study is conducted.
- a justification for, or validation of, the separation technique is provided.

Other considerations

- Algal biomass is determined based on dry weight per volume, or alternatively as cell counts or biovolume using microscopy or an electric particle counter. If an alternative method is used (e.g. flow cytometry, in vitro or in vivo fluorescence, or optical density), a satisfactory correlation with biomass must be demonstrated over the range of biomass occurring in the test.

Your registration dossier provides three OECD TG 201 studies performed on the Substance (study i.) and on the category members PY1 and PY74 (study ii. and iii., respectively) showing the following:

Characterisation of exposure

- for study i., you report that no analytical monitoring of exposure was conducted that "*no suitable method for determination of the test item could be established*" with no further justification;
- for study ii., the analytical monitoring was conducted using HPLC-DAD. The limit of quantification (LOQ) of the method was 100 µg/L. In Section 1 of your CSR, you report that the solubility of the test substance in water is "*13 µg/L at 22-23°C*";
- for study iii., You report that the DOC content of the saturated solution was determined at the start and end of the test;

Additional requirements applicable to difficult to test substances

- the maximum dissolved concentration that can be achieved in the specific test solution is not reported in any of the studies listed above;
- the substances tested in the studies listed above have low solubility and high adsorption potential and therefore losses of the test material may be expected. The result of a preliminary stability study is not reported in any of these studies;
- a justification for, or validation of, the separation technique is not provided for any of the studies listed above.

Other considerations

- for studies i. to iii., biomass was determined based on *in vivo* fluorescence. No data to support the validity of this approach is provided.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the studies included in your registration dossier. More, specifically none of the studies provide adequate information on the characterisation of exposure during the test as no attempt was made to monitor exposure in study i., the sensitivity of the analytical method was too low in study ii., and a nonspecific method (DOC quantification) with low sensitivity was used in study iii.
- Further, in all studies, biomass was determined based on in vivo fluorescence. No justification is provided that this method was adequate for determination of biomass (e.g. evidence of correlation between the measured parameter and dry weight for both control and treated groups). The physiological status of algal cells is known to impact the efficiency of the non-photochemical quenching (NPQ) of fluorescence and differences in physiological status between treatments may bias the relationship between re-emitted fluorescence and biomass;
- you state that "*the test substance is insoluble in water (< 0.1 mg/L)*". While the information on water solubility is not met, as explained in Appendix A.1, WSKOW and WATERNT (from EPISUITE) predict that the water solubility of the Substance and the selected analogue substances is below 1 mg/L. Despite uncertainties, available evidence are robust enough to conclude that these Substances are poorly water soluble;
- the Substance and selected analogue substances are difficult to test (poor water solubility) and the specific requirements of OECD GD 23 are not met for any of the studies, including the estimation of the saturation concentration of the test material in the test medium and the inclusion of a preliminary stability study.

Therefore, the requirements of OECD TG 201 are not met for any of the studies listed above.

B. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. In addition, as already explained under issue A. above, deficiencies were identified on the studies included in your

registration dossier.

On this basis, the information requirement is not fulfilled.

Study design

The Substance is difficult to test due to the low water solubility (below 1 mg/L). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations.
Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

4. Long-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.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided the following information on short-term toxicity testing on aquatic invertebrates:

- a study according to OECD TG 202 on the Substance ([redacted] 2012); study i.
- an adaptation under Annex XI, Section 1.5. In support of your adaptation, you provided the following studies:
  - a study according to OECD TG 202 on PY1 ([redacted], 2004); study ii.
  - a study according to OECD TG 202 on PY97 ([redacted] 2007); study iii.
  - a study according to OECD TG 202 on PY111 ([redacted] 2005); study iv.
  - a study according to OECD TG 202 on PY3 ([redacted] 2004); study v.

You have also provided the following information on long-term toxicity which could be used to cover the information requirement under Section 9.1.1., Column 2:

- an adaptation under Annex XI, Section 1.5. In support of your adaptation, you provided the following studies:
  - a study according to OECD TG 211 on PY1 ([redacted] 2012); study vi.
  - a study according to OECD TG 211 on PY74 [redacted] 1999); study vii.

We have assessed this information and identified the following issues:

A. Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

   As already explained under Appendix A.3., the Substance is poorly water soluble (<1mg/L). Therefore, relevant and reliable information on long-term toxicity on aquatic invertebrates must be provided.

B. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. Therefore, the reported long-term toxicity studies on the analogue substances (i.e. studies vi. and vii.) do not meet the information requirement

On this basis, the information requirement is not fulfilled.

Study design

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section C.3.

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 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 provided the following studies:

1) an OECD TG 473 GLP study (2012) with the analogue PY1 and
2) an OECD TG 487 GLP study (2009) with the analogue PY74.

We have assessed this information and identified the following issue:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation (Annex XI, Section 1.5) is rejected.

On this basis, 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 in bacteria and the *in vitro* cytogenicity test.

i. Triggering of the study

Your dossier contains negative data for an *in vitro* gene mutation study in bacteria and an adaptation for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study, which is rejected for the reasons provided in the Appendix on general considerations and in section 1 of Appendix B.

The result of the request for information in section 1 of Appendix B 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. Information provided

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following studies:

1) an OECD TG 476 GLP study (2011) with the analogue substance PY1;
2) a non-guideline, non-GLP, L5178Y TK +/- mouse lymphoma assay (1987) with the analogue substance PY74.

We have assessed this information and identified the following issue:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation (Annex XI, Section 1.5) is rejected.

On this basis, the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study 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. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

A Short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following studies:

1) an OECD 422 GLP study ([redacted] 2012) with the analogue PY1 via oral (gavage) route in rat;
2) an OECD 408 GLP study ([redacted] 2009) via oral (gavage) with the analogue substance PY74;
3) a non-guideline repeated dose (30 days) toxicity study via oral (feed) route ([redacted] 1970) with the analogue substance PY1;
4) a non-guideline repeated dose toxicity study via oral (gavage) route ([redacted] 1958) with the analogue substance PY3;
5) a non-guideline repeated dose (18 days) via oral (gavage) route ([redacted], 1960) with the analogue substance PY97 ;
6) a non-guideline repeated dose toxicity (30 days) study via oral (feed) route ([redacted] 1971) with the analogue substance PY3;
7) a non-GLP study similar to OECD 407 via oral (gavage) route ([redacted] 1979) with the analogue substance PY1.

We have assessed this information and identified the following issues:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. In addition, as further explained under issue B. below, deficiencies were identified on the studies included in your registration dossier.

B. Annex XI, Section 1.5., the results to be read across must provide adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case OECD TG 407. Therefore, the following specifications must be met:

- at least three dose levels and a concurrent control are tested;
- the highest dose level must aim to induce some systemic toxicity, but not death or severe suffering;
- at least 5 female and 5 male animals are used at each dose level (including the control group);
- the test material is dosed for a period of 28 days until the scheduled termination of the study;
- animals are examined for weight and histopathology (including thyroid gland/ thyroid hormone measurements).

However, the study 4) you have provided was conducted with less than three dose levels. Furthermore, study 4) used less than 10 animals per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 10 animals for each test group set in OECD TG 407. The highest dose level in the study did not induce any systemic toxicity.

Then, for study 5), you report that the exposure duration was 18 days. Therefore, this study is not adequate as it does not cover an exposure duration of at least 28 days.

In addition, studies 3), 6) and 7) are not providing information on the following key investigations: clinical biochemistry, detailed clinical observations, functional observations, reporting of mean and/or individual animal data and ophthalmological examinations (study 7). For none of the studies 3) to 7) information on thyroid gland and thyroid hormone measurements is reported.

Finally, you have not provided a robust summary for sources of information 3) to 6) to demonstrate compliance with the above key parameters and you have identified these studies as reliability 3.

Therefore, the above studies do not have adequate an reliable coverage of the key parameters addressed in the OECD TG 407.

On this basis, the information requirement is not fulfilled.

Annex VIII, Section 8.6.1., Column 2 provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section C.1). According to Annex VIII, Section 8.6.1., Column 2, and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

4. 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 an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following study:

1) an OECD 422 GLP study ([redacted], 2012) with the analogue PY1 via oral (gavage) route in rat;

We have assessed this information and identified the following issue:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation (Annex XI, Section 1.5) is rejected.

On this basis, the information requirement is not fulfilled.

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 administration of the Substance (ECHA Guidance R.7.6.2.3.2.).

5. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following studies:

- a study according to OECD TG 203 on PY74 ([redacted], 2006); study i.
- a study according to OECD TG 203 on PY1 ([redacted] 2012); study ii.

You have not provided information on long-term toxicity which could be used to cover the information requirement on Section 9.1.3., Column 2.

We have assessed this information and identified the following issue:

A. As already explained under Section A.3., the Substance is poorly water soluble. Therefore, for the reasons already explained under Section A.4., relevant and reliable information on long-term toxicity on fish must be provided.

On this basis, the information requirement is not fulfilled.

Study design

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section C.4.

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 an information requirement under Annex IX to REACH (Section 8.6.2.).

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following study:

1) an OECD 408 GLP study ([redacted] 2009) via oral (gavage) with the analogue substance PY74.

We have assessed this information and identified the following issues:

A. *Read-across adaptation*

As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. In addition, as further explained under issue B. below, the study you provided was not conducted using the most appropriate route of exposure for the Substance.

B. *Appropriate route*

Under Annex IX, Section 8.6.2., Column 2, testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

You stated that "[...] *the repeated dose toxicity study, as required in section 8.6.1 of Annex VIII and in section 8.6.2 of Annex IX, does not need to use the inhalation route because exposure of humans via inhalation is considered unlikely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size".*

However, you also report a D50 of 3.4 µm which indicates that the substance is inhalable. No information on uses is provided in the technical dossier and the chemical safety report (CSR). However, you report in the CSR that the most common technical function of the substances are:
- Colouring agents for paints, pigments, plastics and inks
- *"Generally the substances are used in industrial and/or professional settings*
- *The substances are contained in consumer products*
- *The substances are contained in articles handled by consumers".*

The Substance is reported to occur as a powder with a significant proportion of particles of inhalable size (MMAD < 50 µm). Furthermore, the Substance is respirable (D50 = 3.4 µm), has low water solubility (see Section A.3.) and consequently there is a potential for accumulation of the Substance in the lungs.

Moreover, you have not provided any exposure assessment in your dossier or CSR to support that exposure of humans via inhalation is unlikely. The technical functions of the Substance indicate that exposure of professionals and consumers is likely. On the basis of the particle size of the Substance and on the limited information provided on uses, we consider that human exposure to the Substance via the inhalation cannot be

ruled out. Based on the above, the inhalation route is considered to be the most appropriate route of exposure.

On this basis, the information requirement is not fulfilled.

Study design

As explained above, based on the information in the dossier and following the criteria provided under Annex IX, Section 8.6.2, Column 2, the inhalation route is the most appropriate route of administration to investigate repeated dose toxicity for the Substance. Therefore, the sub-chronic toxicity study must be performed according to the OECD TG 413, in rats and with administration of the Substance by inhalation.

Additional parameters

There is evidence that the lower respiratory tract is the primary site of deposition and retention of the Substance, because the Substance is in the form of particle of respirable size.

You are reminded that several paragraphs of the OECD TG 413 address specific issues related to testing of poorly soluble solid aerosols. Details on measurement and evaluation of lung burden are also provided in the OECD GD 39.

Therefore, you are requested to perform measurements of lung burden and bronchoalveolar lavage fluid (BALF) which are specifically designed to address such situation. The latest guidance on how to perform such measurements are described in the revised version of the OECD 413 test guideline adopted on 25 June 2018.

2. Pre-natal developmental toxicity study in one species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

You have adapted the information requirement according to Annex XI, Section 1.2. ('Weight of evidence'). In support of your adaptation, you have provided the following sources of information:

Information on analogue substances:

(i) an OECD 422 GLP study ([redacted], 2012) with the analogue PY1 via oral (gavage) route in rat;
(ii) an OECD 408 GLP study ([redacted] 2009) via oral (gavage) with the analogue substance PY74.

Information on the Substance:

(iii) *"sufficient weight of evidence from several independent sources of information leading to the conclusion that the substances of this category do not cause developmental toxicity and thus does not have to be classified"* as specified below:

a) an acute oral study according to OECD TG 423 ([redacted] 2012);
b) a skin irritation study according to OECD TG 439 ([redacted], 2012);
c) an eye irritation study according to OECD TG 405 ([redacted] 2012);
d) a skin sensitisation study according to OECD TG 429 ([redacted] 2012).

Based on the sources of information under (i.) to (iii.), you argue that the available data gives sufficient information to conclude on the first species prenatal developmental toxicity because

- *"no lethal effects after single oral* [...] *or dermal dose"*;
- "[the category members] *do not have to be classified as eye or skin irritating* [...] or

skin sensitizing";
- "[the category members] *caused no relevant systemic toxic effects in several subacute oral studies in rats* [...] *and in a subchronic oral toxicity study in rats"*;
- "[the category members] *caused no systemic toxic effects in a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test"*;
- "[the category members] *do not interact with living cells/tissues";*
- *"it is unlikely that the substances of this category become systemically bioavailable due to their extremely low solubility in water and low solubility in n-octanol. It can therefore be concluded with sufficient certainty that the substances of this category will not cause developmental toxicity and that testing carried out on one or two species in a Prenatal Developmental Toxicity Study is not scientifically necessary".*

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 adaptation.

While you have listed various risk-related aspects (i. to iii.) to justify you adaptation, you have not included a justification with an assessment, integration and weighing of the individual sources of information for relevance, reliability, coverage, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Your adaptation is rejected because lack of adequate and reliable (concise) documentation for justification and the information requirement is not fulfilled.

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 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects must be covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

We assessed the information provided by you in support of your adaptation and identified the following issues:

Key elements/key investigations: *Prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy*

1) Prenatal developmental toxicity includes information on embryonic/foetal survival

(number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal) after exposure *in utero*.

2) Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs.

3) Maintenance of pregnancy includes information on abortions or early delivery as a consequence of gestational exposure.

The source of information (i.) provides relevant information on developmental toxicity, maternal toxicity and maintenance of pregnancy. In more details, it provides some information on developmental toxicity covering some aspects such as survival, body weights, clinical signs and anogenital distance investigated during postnatal period up to PND 4. However, it does not cover all relevant and essential aspects as defined above as it does not inform on structural malformations and variations (external, visceral and skeletal) as required in OECD TG 414. Furthermore, the reliability of this study to inform on the properties of the Substance is significantly affected by the deficiencies identified in Section 1 of the Appendix on General considerations ('Assessment of your read-across approach for the category of Monoazo Yellow Pigments').

Information sources (ii. and iii.) do not provide any relevant information related to information requirement because eye and skin irritation, acute, sub-chronic studies do not investigate developmental toxicity at all, and low absorption do not inform on developmental toxicity properties.

Conclusion

Taken together, even if study (i.) provides information on pre-natal developmental toxicity, none of sources of information cover structural malformations and variations (external, visceral and skeletal). Furthermore, the reliability of study (i.) is affected so significantly that it cannot be taken into consideration in a weight of evidence approach.

On the basis of the information, 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 OECD TG 414. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Study design

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral administration of the Substance (ECHA Guidance R.7.6.2.3.2.).

3. Long-term toxicity testing on aquatic invertebrates

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

You have adapted this information requirement under Annex XI, Section 1.5 ('Grouping of substances and read-across approach'). In support of your adaptation, you provided the following study:

- a study according to OECD TG 211 on PY1 ([redacted], 2012); study i.
- a study according to OECD TG 203 on PY74 ([redacted], 1999); study ii.

We have assessed this information and identified the following issues:

A. As explained in the Appendix on Reasons common to several requests your read-across adaptation under Annex XI, Section 1.5 is rejected. In addition, as further explained under issue B. below, deficiencies were identified on the studies included in your registration dossier.

B. Under Annex XI, Section 1.5., the results to be read across must provide 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 211 and OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test.. Therefore, the following specifications must be met:

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (*i.e.* detection and quantification) and working range must be available. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
- In semi-static tests, if the concentration of the test material is not expected to remain within ± 20 % of the nominal concentration, then all test concentrations must be determined when freshly prepared and at the time of renewal on one occasion during each week of the test;

Additional requirements applicable to difficult to test substances

- if the test material is poorly water soluble, the maximum dissolved concentration that can be achieved in the specific test solution under the test conditions is determined;
- if losses of the test material are expected within the timeframe of the test, a preliminary stability study is conducted.
- a justification for, or validation of, the separation technique is provided.

Your registration dossier provides two OECD TG 211 on the category members PY1 and PY74 (study i. and ii., respectively) showing the following:

Characterisation of exposure

- for study i., the analytical monitoring was conducted using HPLC-DAD. The limit of quantification (LOQ) of the method was 100 µg/L. In Section 1 of your CSR, you report that the solubility of the test substance in water is "*13 µg/L at 22-23°C*";
- for study ii., you report that no analytical monitoring of exposure was conducted that "*no suitable method for determination of the test item could be established*" with no further justification;

Additional requirements applicable to difficult to test substances

- the maximum dissolved concentration that can be achieved in the specific test solution is not reported in any of the studies listed above;
- the substances tested in the studies listed above have low solubility and high adsorption potential and therefore losses of the test material may be expected. The result of a preliminary stability study is not reported in any of these studies;
- a justification for, or validation of, the separation technique is not provided for any of the studies listed above.

Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More, specifically none of the studies provide adequate information on the

characterisation of exposure during the test as no attempt was made to monitor exposure in study ii. and the sensitivity of the analytical method was too low in study i.;
- the Substance is difficult to test (poor water solubility) and there are critical methodological deficiencies resulting in the rejection of the study results.

Therefore, the requirements of OECD TG 211 are not met for any of the studies listed above.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.3.

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, Column 2. In support of your adaptation, you provided the following justification: "*CSA does not indicate need for further investigations*".

We have assessed this information and identified the following issue:

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

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.

Study design

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section A.3.

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[2].

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[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix E: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2019.

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 27 February 2020.

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

ECHA did not receive any comments within the notification period.

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

ECHA received a proposal for amendment of the deadline set for provision of the information on the water solubility and Partition coefficient n-octanol/water (requested under A.1 and A.2) and accordingly modified the deadline set by the draft decision for provision of that information.

ECHA invited you to comment on the proposed amendment and referred the modified draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-73 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix F: List of references - ECHA Guidance[4] 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)[5]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[5]

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[6]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[6] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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.