EUROPEAN CHEMICALS AGENCY

Helsinki, 20 February 2020

Addressees
Registrants of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
10/06/2015

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 5,12-dihydroquino[2,3-b]acridine-7,14-dione
EC number: 213-879-2
CAS number: 1047-16-1

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***25 November 2022***.

A. Requirements applicable to 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) with the Substance;

2. Only if a negative result in Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance;

3. Justification for an adaptation of a Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.) based on the study requested under Section B.1; with the Substance;

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

B. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method OECD TG 413) in rats with the Substance;

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance;

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.

To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa.

Registrants are only required to share the costs of information that they are must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

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 general considerations

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

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

- 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.) if a negative result in Annex VIII, Section 8.4.2. is obtained.
- 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.)

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

Grouping of substances and read-across approach

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

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

A. Scope of the grouping

i. Description of the grouping

In your registration dossier you refer to a category of 'Quinacridone pigments'. You have provided a read-across/category justification documentation in sections of the CSR (toxicokinetic, discrete endpoints).

For the purpose of this decision, the following abbreviations are used for the group members:

	Abbreviation/Name	Numerical ID
1)	PY282/Pigment yellow 282	EC 909-082-0
2)	4,11-Dichloro-Quinacridone	EC 221-423-9
3)	PV19/Pigment violet 19	EC 213-879-2
4)	PR122/Pigment red 122	EC 213-561-3
5)	PR202/Pigment red 202	EC 221-424-4
6)	PR209/Pigment red 209	CAS 3573-01-1

As reasons for grouping the substances you argue that they are not bioavailable and thus of no toxicological relevance due to their low solubility in different media and large molecular size.

You define the the structural basis for the grouping as *"the basic Quinacridone structure (5,12-Dihydroquino[2,3-b]acridine-7,14-dione) and at most two substituents (1-2 methyl groups or 2 chlorine atoms). Excluded are Quinacridones substituted by substituents other than methyl and chloro."* ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

B. Predictions for properties

You have provided the following reasoning for the prediction of toxicological properties: *"all members are of high structural similarity with only very minor differences in their physico-chemical properties [...] have a low solubility in water (predominantly <35µg/L, [...]) and show no adverse effects in toxicological and ecotoxicological studies."* Further, *"available experimental data indicate that the Quinacridone Pigments of this category are not taken up by the body/organism after ingestion, inhalation or skin contact."*

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

You intend to predict the properties for the category members from information obtained from valid and reliable studies with the following category members:

I. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.), conducted similar or according to OECD TG 471 with the substances:
   a. 2x PR202 (EC 221-424-4), 1992, 1995
   b. 2x PR122 (EC 213-561-3), 2007, 2001
   c. 2x PV19 (EC 213-879-2), 2005, 2004
   d. PR282 (EC 909-082-0), 2004
   e. PR209 (CAS 3573-01-1), 2003

II. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.), conducted similar or according to OECD TG 473 with the substances:
   a. PR202 (EC 221-424-4), 1995
   b. PR122 (EC 213-561-3), 1991
   c. PR282 (EC 909-082-0), 2005

III. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), conducted similar or according to OECD TG 476 with the substances:
   a. PR202 (EC 221-424-4), 1995
   b. PR122 (EC 213-561-3), 1991

IV. Repeated dose toxicity (Annex VIII-IX, Section 8.6)
   a. PR122 (EC 213-561-3), sub-chronic (90d) repeated dose toxicity study (OECD TG 408), 2006
   b. PR282 (EC 909-082-0), sub-acute (28d) repeated dose toxicity study (OECD TG 407), 2005
   c. PR209 (CAS 3573-01-1), sub-acute (30d) repeated dose toxicity study (pre-guideline), 1971

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

1. *Missing supporting information*

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". Within this documentation "*it is important to provide supporting information to strengthen the rationale for the read-across*"[2]. 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).

"*Adequate and reliable documentation*" must include

i. supporting (toxicokinetic) information on the absence of bioavailability and
ii. bridging studies to compare such properties of the 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 substance is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies, and from studies demonstrating absence of bioavailability.

Supporting (toxicokinetic) information on the absence of bioavailability

In your read-across hypothesis, you state that the category members have comparable physico-chemical properties, as well as low solubility in water and organic solvents, which results in a very low bioavailability and thus no or low toxicity. Furthermore, you have submitted short-term toxicity studies on three of six category members, PR122, PR282 and PR209, which demonstrate no effect levels at the limit dose of at least 1000 mg/kg bw/d. Furthermore, you have submitted toxicokinetic studies (reliability score 4; not assignable) with PV19 and information from an investigative non-guideline study ([redacted] 2009) with PR122. This data set reported in the technical dossier does not include relevant, reliable and adequate information for the target and the source substances to support your read-across hypothesis.

In your comments to the draft decision

- accept that "*a complete proof of the hypothesis is yet not available [...]*"
- you refer to the absence of systemic or reproductive toxicity in numerous available repeated dose toxicity and reproductive toxicity studies on structurally variable types of pigments outside the scope of the category which are available in the ECHA database. You state that "*there is no reason to expect a different behavior from the yet untested pigments of the category.*" You did not explain the relevance of the indicated supporting information specifically to qinacridone pigments. For instance, you did not explain how mechanisms other than solubilisation through ionisation would -or would not- contribute to systemic toxicity, and how this allows a prediction of properties of the analogue substances. You also did not include a justification for the selection of the structurally similar pigments to exclude potential bias. You did not provide the related data (e.g. robust study summaries of the relevant studies) in your documentation.
- you indicate your intention to perform static and dynamic dissolution assays to support the claims of poor absorption and low bioavailability, and to acquire the necessary supporting information with regard to your claims on bioavailability.

First, the existing information gives some indications about low bioavailability based on solubility and physico-chemical properties. However, in the absence of data demonstrating absence of bioavailability (e.g. reliable toxicokinetic studies), is not possible to conclude on bioavailability for any of the category members. Your theoretical considerations on the

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

absence of bioavailability have not been substantiated by experimental data such as studies on toxicity after repeated exposure (e.g. OECD TG 407/421/422), and are thus rejected.

Second, it is not possible to conduct an evaluation of the referred supporting information in absence of sufficient documentation and in the absence of an explanation of their relevance for your read-acros adaptation.

Third, it is in your discretion to generate and provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH.

Bridging studies to compare such properties of the category members

You did not provide appropriate bridging studies (such as a screening study OECD TG 421 or 422) to compare the properties of the category members with regard to repeated dose and reproductive/developmental toxicity. As also explained in the next section (data density to derive a regular pattern), your hypothesis of low bioavailability is not supported by results from repeated dose toxicity studies with representative analogue substances across the category.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Based on the provided information in the robust study summaries for the toxicokinetic study conducted with PV19, ECHA is unable to conclude on the reliability of the study and accepts your reliability score. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

2. *Data density to derive a regular pattern*

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.*

According to the ECHA Guidance, one of the factors in determining the robustness of a category is the density and distribution of the available data across the category.[3] To identify a regular pattern and/or to derive reliable prediction of the properties of the members of the category, adequate and reliable information covering the range of structural variations identified among the category members needs to be available.

In your dossier, you have provided the following valid and reliable studies:

1. For *in vitro* genotoxicity with bacteria (Annex VII, Section 8.4.1), five out of six category members have been tested according to OECD TG 471.

2. For *in vitro* chromosomal aberrations in mammalian cells (Annex VIII, Section 8.4.2), three out of six category members have been tested in relevant tests according or similar to OECD TG 473.

3. For *in vitro* gene mutations in mammalian cells (Annex VIII, Section 8.4.3), two out of six category members (PR202, PR122) have been tested according to OECD TG 476.

4. For repeated dose toxicity (Annex VIII, Section 8.6.1 and Annex IX, Section 8.6.2), two category members (PR282, PR209) have been tested in oral short-term (28-day) toxicity studies (OECD TG 407, 2005; pre-guideline study 1971) and one of the

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.1.5.

category members (PR122) in a sub-chronic (90d) toxicity study (OECD TG 408, 2006). No repeated dose toxicity studies by the inhalation route have been provided.

In your comments on the initial draft decision you stress that the three repeated dose toxicity studies included in the dossier, together with 80 repeated dose or reproductive toxicity studies on different types of pigments (studies, together with NOAELs listed in your comments) *all* showing absence of adverse systemic effects "can reasonably be considered representative for the whole category". Futhermore you consider that "*There is no reason to expect a different behavior from the yet untested pigments of the category*".

Based on these studies you claim that there are similar properties between the category members.

The category members have multiple structural differences, but no information has been provided to establish whether and to what extent any of the category members are representative of the whole category or a subset of it. In addition, the available studies cover only a small subset of these structural differences for each endpoint. Information for two (3., above) or three (2., 4., above) category members is not sufficient to conclude which substances are representative of the category members for *in vitro* genotoxicity and repeated dose toxicity in the absence of (lower tier) toxicity studies with all category members for the relevant endpoint.

Regarding your comments, the tables with 80 pigments do not contain any studies performed with quinacridone pigments other than the three repeated dose toxicity studies included in your dossier. All other studies were performed with different analogue substances. No justification for the selection of these substances was provided, and no read-across hypothesis was included. The only information included on the study designs and outcomes are the test guideline, year and NOAEL. No other details on the studies were provided. Based on this limited amount of information it is not possible to make any conclusions on the relevance or reliability of those studies. Based on the limited data on the substances included in your category and missing bridging studies it is not possible to conclude which substances are representative of the category members for repeated dose toxicity.

There are too few data points (i.e. low data density) in the current data matrix for demonstrating consistency and predicting properties for the listed toxicological endpoints as proposed by you. Therefore, the information provided is not sufficient to conclude that toxicological properties are likely to follow a regular pattern.

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

As explained above, you have not established that relevant properties of the registered 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.

(ii) Assessment of the Weight of evidence adaptation under Annex XI, Section 1.2.

You have adapted the information requirements for a screening for reproductive/developmental toxicity study (a standard information requirement in Annex VIII to REACH) and a pre-natal developmental toxicity study in one species (a standard information requirement in Annex IX to REACH) by using weight of evidence (WoE) according to Annex XI, Section 1.2.

In order to allow concluding on no reproductive toxicity (sexual function and fertility, and developmental toxicity) for the substance in a weight of evidence adaptation, the information

in the justification must cover the key elements (parameters) foreseen to be investigated in the screening for reproductive/developmental toxicity study and the PNDT study requested in this decision.

As a justification for your weight of evidence adaptation you provided in your registration dossier:

- Allegation of low toxicity (acute/sub-acute/sub-chronic effects, skin/eye irritation) among category members, which *"indicates that the substances of this category do not interact with living cells/tissues"*
- Allegation of low bioavailability based on a repeated dose toxicity study and low solubility in water and octanol.

In your comments on the initial draft decision, you refer to a table with reproductive toxicity studies performed with different pigments, none of them showing adverse effects and you included a summary table listing 24 studies (OECD TG 414, 415, 421, 422) performed with 23 different pigments, belonging to 19 different pigment classes. The route of administration, NOAEL and study year are specified in that table.

You recognise that *"Even though they did not include specific pathological investigations regarding skeletal or visceral abnormalities, they still did not show any adverse effects on number or well-being of offspring"*. You consider that *"This is a strong indication that no major abnormalities occurred regarding the prenatal development of these animals or the fertility of their parents"*.

However, first, the information from repeated dose toxicity studies, your claim that *"the substances of this category do not interact with living cells/tissues"*, and the solubility data, do not inform on intrinsic hazardous properties of the Substance regarding reproductive toxicity.

Second, the studies included in your dossier give some indication of low toxicity of the substances, but you did not provide any justification for your claim that there is no interaction with living cells or tissues. The low solubility in water and octanol does not always mean that the substances have low solubility in biological fluids and are not bioavailable. In the absence of data demonstrating absence of bioavailability, it is not possible to conclude on bioavailability for all of the category members.

Third, you provided statements and studies that do not investigate and/or provide key elements for developmental toxicity or sexual function and fertility by mating and producing offspring. Specifically, there is no information on growth, survival, external, skeletal and visceral alterations in the developing foetuses and their relationship to maternal toxicity (key elements (parameters) in the pre-natal developmental study). Regarding sexual function and fertility and toxicity to offspring, and their relationship to systemic toxicity, there is, among others, no information on key elements (parameters) of the screening for reproductive/developmental toxicity study (functional fertility (mating, gestation, delivery and lactation) and histoapthology of the reproductive organs and tissue). In the absence of any information that is specifically required under the corresponding information requirements, your weight of evidence adaptations for Annex VIII, section 8.7.2. and Annex IX, section 8.7.2 are rejected and the information requirements are not met.

Fourth, within your weight of evidence adaptation, you refer to several sources of information stemming from substances of you category. However, as explained in this Appendix above, your adaptation using a Grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

The sources of information included in your comments have the following deficiencies affecting their reliability:

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).

i. All studies were performed with analogue substances. No justification for the selection of these substances was provided, and no read-across hypothesis was included. Only one of the substances included in your list of 24 pigments with studies on reproductive toxicity belongs to the group used for the grouping and read-across adaptation in your dossier (rejected for the reasons explained above).
Therefore the provided studies cannot be considered a reliable source of information.

ii. No adequate and reliable documentation of the source studies, in particular no robust study summaries, has been presented. The only information included on the study designs and outcomes are the test guideline, year and NOAEL. No other details on the studies were provided. Based on this limited amount of information it is not possible to conclude on the relevance or reliability of those studies.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 421/422 or TG414 study. Your adaptation is, therefore, rejected.

(iii) Assessment of the column 2 adaptation under Annex IX, Section 8.7.

In your dossier, you intend to demonstrate that your Substance is of low toxicological activity and that no systemic absorption occurs. However, for such adaptation claims the specific adaptation rule at Annexes IX/X, Section 8.7., Column 2, first paragraph, third indent applies. Hence, ECHA assesses below your adaptation according to this specific rule of adaptation.

According to Annex IX, Section 8.7., Column 2, first paragraph, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:

i. that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
ii. that there is no or no significant human exposure.

In your dossier you provided:

i. A sub-chronic study performed with an analogue substance. The study suggests that the absorption of the substance might be low (the substance was not detected in blood and liver samples of exposed animals), but the information provided is not conclusive because it does not include, e.g., how long was the period between the last dose and collection of the samples or elimination rate data. Therefore, the information provided cannot be considered as proof of no systemic absorption.
ii. No detailed information on uses or exposure were included in the dossier. Based on the reported uses as colouring agent and pigment, significant human exposure is, however, likely.

Based on the above, your adaptation is rejected and information requirements are not met.

Appendix A: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. **In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

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

As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

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

2. **Only if a negative result in Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation in bacteria and the *in vitro* cytogenicity tests.

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

As explained in the Appendix on general considerations your adaptation is rejected and the information requirement is not fulfilled.

Your dossier contains negative results from 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 A.

The result of the requests for information in sections 1. of Appendix A 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.

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.

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

3. **Justification for an adaptation of the Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)**

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

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

As explained in the Appendix on general considerations your adaptation is rejected.

Therefore, the information requirement is not fulfilled.

Column 2 of Annex VIII, Section 8.6.1., 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 Column 2 of Annex VIII, Section 8.6.1., 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 (Annex VIII, Section 8.7.1.)

A Screening for reproductive/developmental toxicity study (OECD TG 421 or 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. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement by using weight of evidence (WoE) according to Annex XI, Section 1.2. and ECHA understands that you have also adapted this information requirement by using an adaptation under Annex X, Section 8.7.2, column 2.

As explained in the Appendix on general considerations your WoE adaptation is rejected, the Annex IX column 2 adaptation is not available at Annex VIII, and therefore the information requirement is not fulfilled.

A study according to the test method OECD TG 421/422 should be performed in rats with oral[4] administration of the Substance.

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

Appendix B: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to REACH.

1. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.)**

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

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 and by providing an adaptation according to Annex IX, Section 8.6.2, Column 2. You provided a sub-chronic repeated dose oral toxicity (OECD TG 408) study, a sub-acute oral repeated dose toxicity (OECD TG 407) study, and a non-guideline short-term repeated dose toxicity study with analogue substances.

As explained in the Appendix on general considerations above, your adaptation is rejected.

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the inhalation route is the most appropriate route of administration to investigate repeated dose toxicity[5]. The sub-chronic toxicity study must be performed according to the OECD TG 413, in rats and with administration of the Substance by inhalation.

You argue that "*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 did not provide any justification or documentation for this claim.

Although no details on uses (PROCs) or exposure were included in the dossier, the information provided in the technical dossier and the chemical safety report on properties of the Substance and its uses (professional and consumer uses as colouring agents and pigments) indicate, however, that human exposure to the Substance by the inhalation route is likely. More specifically, the Substance is reported to occur as a dust with a significant proportion [redacted] of particles of inhalable size [redacted]

There is evidence that the lower respiratory tract is the primary site of deposition and retention of the Substance, because it is poorly soluble in water and respirable (D50 5.8 µm). 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 (Annex IX, Section 8.7.2.) in a first species**

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

[5] ECHA Guidance R.7a, Section R.7.5.4.3.

You have adapted this information requirement by using weight of evidence (WoE) according to Annex XI, Section 1.2. and ECHA understands that you have also adapted this information requirement by using an adaptation under Annex X, Section 8.7.2, column 2.

As explained in the Appendix on general considerations your adaptations are rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[6] administration of the Substance.

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

Appendix C: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 14 January 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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

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

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

Appendix D: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

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

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

   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: 'How to report robust study summaries'[7].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

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

5. List of references of the ECHA Guidance and other guidance/ reference documents[9]

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[10]

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.

OECD Guidance documents[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

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

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.