

Helsinki, 18 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

22/03/2013

Registered substance subject to this decision, hereafter 'the Substance'

Substance name: N,N'-(2,5-dichloro-1,4-phenylene)bis[4-[[2-chloro-5-(trifluoromethyl)-phenyl]azo]-3-hydroxynaphthalene-2-carboxamide]

EC number: 257-776-0

CAS number: 52238-92-3

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 **23 November 2022**.**A. Requirements applicable to all the Registrants subject to Annex VII of REACH**

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance;

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

1. Only if a negative result in Annex VII, Section 8.4.1. 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;
2. 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 C.1.; with the Substance;
3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

C. 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. The study must include measurements of lung burden and bronchoalveolar lavage fluid (BALF) analysis as described in the current version (25 June 2018) of the OECD TG 413.
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 Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- 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 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>.

Authorised¹ 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 gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- 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.
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 'disazocondensation red 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	CAS number
1) PB23 /Pigment Brown 23	35869-64-8
2) PB41 /Pigment Brown 41	68516-75-6
3) PR144 /Pigment Red 144	5280-78-4
4) PR166 /Pigment Red 166	3905-19-9
5) PR214 /Pigment Red 214	40618-31-3
6) PR220 /Pigment Red 220	68259-05-2
7) PR221 /Pigment Red 221	71566-54-6
8) PR242 /Pigment Red 242	52238-92-3
9) PR262 /Pigment Red 262	79665-24-0

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 structural basis for the grouping as "disazocondensation red pigments". ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

In your comments to the draft decision you clarify that "*no substances providing useful data were excluded from the assessment*", and that your intention is not to define a category but to use "*read-across approach*" to adapt individual information requirements. You further explain the structural similarities and differences of the selected analogue substances in your comments. ECHA acknowledges your clarifications. On that basis, ECHA understands that you submitted an analogue approach. The basis for predictions, which apply to an analogue approach as part of a read-across adaptation, is discussed further below under B. *Predictions for properties*; these additional explanations do not change the outcome of ECHA's assessment.

B. Predictions for properties

You have provided the following reasoning for the prediction of toxicological properties: The "*category hypothesis is fundamentally based on the low bioavailability. None of the pigments are sufficiently soluble either in water or in octanol for systemic uptake or metabolism.*" [...] You argue this based on the molecular weight (██████████) and modelled rigidity of the structures, low solubility (<0.1 mg/L) and "*no increased solubility or degradation in stomach acid is possible.*" You further consider a potential metabolism of the analogue substances, which would lead to metabolites of higher toxicity.

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

You intend to predict the properties for the analogue substances from information obtained from valid studies² with the following analogue substances:

- I. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.) similar or according to OECD TG 471:
 - a. PR144 (CAS 5280-78-4), 2006
 - b. PR166 (CAS 3905-19-9), 2006
- II. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.) similar or according to OECD TG 473
 - a. PR242 (CAS 52238-92-3), 1992
- III. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) similar or according to OECD TG 476.
 - a. PR166 (CAS 3905-19-9), 1989
- IV. Repeated dose toxicity (Annex VIII-IX, Section 8.6)
 - a. PR166 (CAS 3905-19-9) according to OECD TG 407, 2009
 - b. PR220 (CAS 68259-05-2), according to OECD TG 422, 2012

² You have provided further *in vivo* cytogenicity studies, but these studies are not relevant for the endpoints for which you claim a read-across. Therefore, these studies have not been assessed. You have also provided *in vivo* gene mutation studies in mammals, but these studies are not appropriate for the reasons explained under endpoint section below.

- V. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1) and Prenatal developmental toxicity (Annex IX, Section 8.7.2)
- a. PR220 (CAS 68259-05-2), according to OECD TG 422, 2012

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*"³. 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 information on the absence of bioavailability and
- ii. bridging studies to compare such properties of the analogue substances.

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 information on the absence of bioavailability

In your read-across hypothesis, you state that the analogue substances have a molecular weight between [REDACTED], 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 two of nine analogue substances, PR166 and PR220, which demonstrate no effect levels at the limit dose of 1000 mg/kg bw/d.

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*" but that "*consideration of all available information led the authors of the dossier to the conclusion that the hypothesis of "no bioavailability" is plausible.*"
- 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 selected analogue substances 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 disazocondensation red 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

³ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

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 molecular size and solubility. However, in the absence of data demonstrating absence of bioavailability (e.g. toxicokinetic studies), it is not possible to conclude on bioavailability for any of the analogue substances. Furthermore, the fact that the analogue substances PB 23 and PR 166 have been tested positive in ames tests only in presence of metabolic activation suggest that enzymatic metabolism can be relevant for the analogue substances tested. Your theoretical considerations on the 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-across 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 analogue substances

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

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. The allegation on potential metabolism is unsubstantiated, without further explanation on its impact on the prediction of hazardous effects by potentially bioavailable parent substance.

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.*"

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance⁴ and related documents^{5, 6}. To identify a regular pattern and/or

⁴ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

⁵ Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: [Read-Across Assessment Framework \(https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across\)](https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

⁶ Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: <https://doi.org/10.2823/794394>

to derive reliable prediction of the properties of the analogue substances, adequate and reliable information covering the range of structural variations identified among the analogue substances needs to be available.

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

1. For *in vitro* genotoxicity with bacteria (Annex VII, Section 8.4.1), two out of nine analogue substances (PR144 and PR166) have been tested according to OECD TG 471 with modified metabolic activation for azo-substances, such as the analogue substances, whereas all other bacterial tests are invalid because they are without this relevant modification.
2. For *in vitro* chromosomal aberrations in mammalian cells (Annex VIII, Section 8.4.2 and 8.4.3), one out of nine analogue substances (PR242) has been tested (OECD TG 473).
3. For *in vitro* gene mutations in mammalian cells, one out of nine analogue substances (PR166) has been tested (OECD TG 476).
4. For repeated dose toxicity (Annex VIII, Section 8.6.1 and Annex IX, Section 8.6.2), one analogue substance (PR166) has been tested in an oral short-term (28-day) toxicity study (OECD TG 407, 2009) and one of the analogue substances (PR220) in a combined repeated dose toxicity and screening for reproductive/developmental toxicity (OECD TG 422, 2012). No repeated dose toxicity studies by the inhalation route have been provided. No sub-chronic toxicity studies (90-day) have been provided.
5. For screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1) and pre-natal developmental toxicity (Annex IX, Section 8.7.2), one of nine analogue substances (PR220) has been tested in a combined repeated dose toxicity and screening for reproductive/developmental toxicity (OECD TG 422, 2012). No pre-natal developmental toxicity studies have been provided.

In your comments on the initial draft decision you stress that the two 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 group*". Furthermore 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 analogue substances.

The analogue substances have multiple structural differences, but no information has been provided to establish whether and to what extent any of the analogue substances 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 (1.+4., above) or one (2., 3.+5., above) analogue substances is not sufficient to conclude which substances are representative of the analogue substances for *in vitro* genotoxicity, repeated dose toxicity and toxicity to reproduction and pre-natal development in the absence of (lower tier) toxicity studies with all analogue substances for the relevant endpoint.

Regarding your comments, the tables with 80 pigments do not contain any studies performed with disazocondensation red pigments in addition to the two 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 analogue substances and missing bridging studies, it is not possible to conclude which substances are representative of the analogue substances for repeated dose toxicity.

Considering the distinct structural differences between the analogue substances, 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. According to Annex XI Section 1.5 properties of the target substance may be predicted *"if these are likely to follow a similar or 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.

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

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

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided a key study and supporting studies in your dossier:

- i. Key study: *In vitro* gene mutation study in bacteria (1991) according to OECD TG 471.
- ii. Supporting study: *In vitro* gene mutation study in bacteria (1979) according to OECD TG 471.

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

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). The key parameter(s) of this test guideline include:

- a) If the Substance is an azo-dye or a diazo-compound, the test in presence of metabolic activation must be performed following the Prival modification.
- b) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 *uvrA* or *E. coli* WP2 *uvrA* (pKM101)

The reported data for the studies you have provided did not include

- a) the Prival modification, in spite of the fact that the tested substance is a diazo-compound
- b) key study: the appropriate 5 strains, as the information provided does not include results in the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 *uvrA* or *E. coli* WP2 *uvrA* (pKM101).

Therefore, the information provided does not cover a key parameter required by OECD TG 471.

In addition, 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.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, 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 the REACH Regulation.

1. Only if a negative result in Annex VII, Section 8.4.1. 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 test.

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. The valid *in vitro* gene mutation study in mammalian cells with PR166 and the *in vivo* genotoxicity studies with PB23 and PR166, which are considered inappropriate for this endpoint because they are only indicators of DNA lesions or non-guideline studies, cannot be used to adapt the information requirement for *in vitro* gene mutation in mammalian cells. Therefore, the information requirement is not fulfilled.

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

The information for the *in vitro* gene mutation study in bacteria is rejected for the reasons provided in section 1. of Appendix A.

The result of the request for information in section 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.

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.

2. 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 the standard information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained under Appendix General considerations, your adaptation according to Annex XI, Section 1.5 is rejected, and 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 1 of Appendix C). 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.

3. 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.

Grouping approach in the registration dossier

In your registration dossier, you have adapted the standard information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained under Appendix General considerations, your adaptation according to Annex XI, Section 1.5 is rejected, and the information requirement is not fulfilled.

In your comments on the initial draft decision you agree that *"From a purely formal point of view, it is true that only one specific study on fertility and prenatal development has been provided"* for the substances included in the group. Furthermore, you refer to your hypothesis on low bioavailability of the substances in the group and state that *"the performance of in vivo studies on fertility and pre- and post-natal development involving very high numbers of animals is considered as scientifically not justified"*.

The reasons for the rejection of your adaptation according to Annex XI, Section 1.5 are presented in the Appendix General considerations.

Weight of the evidence in your comment

In your comments on the initial draft decision, ECHA understands that you have provided a weight of the evidence adaptation under Annex XI, section 1.2 of REACH. You have not submitted any explanation why the sources of information provide sufficient weight of evidence. This is a critical deficiency under Annex XI, section 1.2 which requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You refer to 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. These findings in combination with the known lack of toxicity and the conviction described above that the investigated pigments are not or only very little bio-available were*

considered sufficient to waive the in vivo studies on reproductive toxicity involving high numbers of animals for reasons of animal welfare”.

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

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

First, your claim on “*very little bio-available*” is not supported by data demonstrating absence of bioavailability (e.g. toxicokinetic studies). Thus it is not possible to conclude on bioavailability or on the relevance of your statement.

Second, the sources of information have the following deficiencies affecting their reliability:

- i. 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).

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

A study according to the test method OECD TG 421/422 should be performed in rats with oral⁷ administration of the Substance.

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

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, 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 the REACH Regulation.

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 the information requirement according to Column 2 of Annex IX, Section 8.6.2. based on not significant systemic uptake and no indication of toxicity observed in a study according to OECD TG 422 study and in a study according to OECD TG 407 with analogue substances.

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

Annex IX column 2 adaptation not met

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil the following criteria, including:

- i. the Substance is not inhalable and
- ii. no evidence of absorption, and no evidence of toxicity in a 28-day 'limit test',
- iii. particularly if such a pattern is coupled with limited human exposure.

You have not demonstrated that all criteria are met:

- (i) The data provided in your dossier indicate that the Substance is inhalable (as discussed further below).
- (ii) You did not demonstrate that there is no evidence of absorption. More specifically, the OECD TG 407 and 422 studies are inconclusive information and cannot be considered as no evidence of absorption because the studies did not investigate toxicokinetic properties such as absorption. Furthermore, the submitted toxicity studies (OECD TG 407 and OECD TG 422) were performed with analogue substances. As explained under Appendix General considerations, your adaptation according to Annex XI, Section 1.5 is rejected. Therefore the studies cannot be used to demonstrate that there is no evidence of toxicity.
- (iii) Human exposure is likely because widespread uses, including professional and consumer uses are reported.

Therefore, your adaptation is rejected.

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

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 toxicity⁸. The sub-chronic toxicity study must be performed according to the OECD TG 413, in rats and with administration of the Substance by inhalation. The information provided in the technical dossier and the chemical safety report on properties of the Substance and its uses indicate that human exposure to the Substance by the inhalation route is likely. More specifically, uses of the Substances as colouring agents and pigments for paints, plastics and inks in industrial

⁸ ECHA Guidance R.7a, Section R.7.5.4.3.

and/or professional settings and in consumer products have been reported. The Substance is reported to occur as a dust with a significant proportion of particles of inhalable size. Furthermore, based on the information provided on the particle size distribution (), the Substance is assumed to be respirable (particle size distribution information adaptation according to Annex XI, Section 1.5 provided) and is of low water solubility. Consequently there is a potential for accumulation of the substance in the lungs. The test must be therefore performed by the inhalation route using the test method OECD TG 413.

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. 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.

You have adapted the information requirement according to Column 2 of Annex IX, Section 8.7. based on lack of toxicity and absorption, and no significant human exposure of the general population. You have also provided an OECD 422 study with an analogue substance.

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

Column 2 adaptation

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

- i. that there is no evidence of toxicity seen in any of the tests available; and
- ii. that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- iii. that there is no or no significant human exposure.

You have not demonstrated that all criteria are met:

- (i) the submitted toxicity studies such as the sub-acute toxicity study (OECD TG 407) and the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422) were performed with analogue substances. As explained under Appendix General considerations, your adaptation according to Annex XI, Section 1.5 is rejected. Therefore the studies cannot be used to demonstrate that there is no evidence of toxicity.
- (ii) You have not provided any toxicokinetic data to prove that no systemic absorption occurs. The OECD TG 422 and OECD TG 407 studies, or any provided studies, did not investigate toxicokinetic properties such as absorption.
- (iii) Furthermore, as discussed under section 1 of Appendix C, the uses of the Substance you identified indicate that there is a possibility of significant human exposure.

OECD TG 422 study does not fulfill the requirement

To be considered compliant and enable assessing if the Substance is a developmental toxicant, the information provided has to meet the requirements of OECD TG 414 in one species.

You have not provided information following OECD TG 414. Instead, you have provided an OECD TG 422 study. In this study, structural malformations and variations are not investigated as required in the PNNT study (OECD TG 414). Therefore, this study does not fulfil the information requirement.

Weight of the evidence in your comment

In your comments on the initial draft decision, ECHA understands that you have provided a weight of the evidence adaptation under Annex XI, section 1.2 of REACH.

You refer to twenty-four reproductive toxicity studies performed with different pigments, none of them showing adverse effects and you included a summary table listing 24 studies (OECD TGs 414, 415, 421, 422) performed with 23 different pigments, belonging to 19 different pigment classes. Route of administration, NOAEL and 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. These findings in combination with the known lack of toxicity and the conviction described above that the investigated pigments are not or only very little bio-available were considered sufficient to waive the in vivo studies on reproductive toxicity involving high numbers of animals for reasons of animal welfare"*.

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

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

First, your claim on *"very little bio-available"* is not supported by data demonstrating absence of bioavailability (e.g. toxicokinetic studies). Thus it is not possible to conclude on bioavailability or on the relevance of your statement.

Second, these sources of information have the following deficiencies affecting their reliability:

- i. 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).

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. Furthermore, as discussed in the Appendix General considerations, in the absence of data demonstrating absence of bioavailability, it is not possible to conclude on bioavailability for any of the analogue substances.

- ii. No adequate and reliable documentation of the source studies has been presented. The only information included on the study designs and outcomes are the test guideline, year and NOAEL. You mention that "*they did not include specific pathological investigations regarding skeletal or visceral abnormalities*". 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.
- iii. In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The key parameter(s) of this test guideline include e.g.: examination of the fetuses for sex and body weight/external, skeletal and soft tissue alterations (variations and malformations)/number of resorptions and or live fetuses/ measurement of anogenital distance in live rodent fetuses.
As you indicate, the sources of information "*did not include specific pathological investigations regarding skeletal or visceral abnormalities*" and, therefore, they do not cover the required key parameter.

As a conclusion, the sources of information as indicated above are not reliable.

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 414 study. Therefore, your adaptation is rejected.

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

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral⁹ administration of the Substance.

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

Appendix D: 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 17 January 2019.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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) or 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. 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 E: 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'¹⁰.

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 PPOD dossiers"¹¹.

5. List of references of the ECHA Guidance and other guidance/ reference documents¹²

¹⁰ <https://echa.europa.eu/practical-guides>

¹¹ <https://echa.europa.eu/manuals>

¹² <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

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)¹³

Physical-chemical properties

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment

Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents¹⁴

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.

¹³ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

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

Appendix F: 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 fulfilled
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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