EUROPEAN CHEMICALS AGENCY

Helsinki, 8 November 2019

Addressee: [redacted]

Decision number: CCH-D-2114488728-27-01/F
Substance name: 2,9-dimethylanthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone
EC number: 226-866-1
CAS number: 5521-31-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/04/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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 registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance provided that the study requested under 1. has negative results;**

3. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

4. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats with the registered 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 test guideline;**

5. **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 registered substance;**

You are required to submit the requested information in an updated registration dossier by ***16 May 2022***. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

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] by Wim De Coen, Head of Unit, 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 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Grouping of substances and read-across approach

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation.

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for several endpoints, including:

- *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.);
- *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);
- screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.); and
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).

ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the information request for the individual endpoints.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category.

Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus,

physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[2, 3] - (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read across.

A. Scope of the category

You have provided a category documentation as part the CSR (Annex I).

You have defined the structural basis for the category/grouping as substances which are based on a perylene tetracarboxyl group as common structural moiety. You indicated the following applicability domain: *"This category covers inert solid pigments derived from a central perylenetetracarboxyl moiety which differ from one another by the various substitutions"*.

You have identified the following substances as 'Perylene pigments' category members:

[1] *Perylimid (Pigment Violet 29)* : Perylene-3,4:9,10-tetracarboxydiimide (EC No 201-344-6)

[2] *Per acid (Pigment Red 224):* Perylene-3,4:9,10-tetracarboxylic dianhydride (EC No 204-905-3)

[3] *Pigment red 178:* 2,9-bis[4-(phenylazo)phenyl]anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 221-264-5)

[4] *Pigment red 149:* 2,9-bis(3,5-dimethylphenyl)anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 225-590-9)

[5] *Pigment red 179:* 2,9-dimethylanthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline - 1,3,8,10(2h,9h)-tetrone (EC No 226-866-1)

[6] *Pigment black 31:* 2,9-bis(2-phenylethyl)anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 266-564-7)

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

[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://echa.europa.eu/publications/technical-scientific-reports

[7] *Pigment black 32:* 2,9-bis(p-methoxybenzyl)anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 280-472-4)

[8] *Perylene black I:* [redacted] (EC No 479-300-2)

[9] *Perylene black II:* [redacted] (EC No 475-310-6)

ECHA notes the following shortcomings with regards to your category definition.

Applicability domain of the category

According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.4.1, (version 1.0, May 2008) a category hypothesis should address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint. These rules, can be described as the applicability domain for an endpoint and provide a means of extending the category membership to chemicals not explicitly included in the current definition of a category.*"

Based on your description of the structural basis of your grouping/category approach, ECHA understands that all category members share a common 'core structure' and that they vary only in terms of their substitutions on the perylene tetracarboxyl moiety.

In your revised category justification documentation, submitted as an attachment to your comments to the initial draft decision, you provided a detailed description of the applicability domain. The category covers solid pigments derived from a central perylene moiety with a hexacyclic structure attached at both positions 6-27 and 13-18 which differ by the nature of the atom at the "Q" positions (either oxygen or nitrogen) and by substitutions at "Q" positions. ECHA notes you have now defined the allowed substitutions on the core structure. ECHA considers that the inclusion and exclusion criteria are also clearly defined in your comments.

B. Prediction of toxicological properties

You have provided the following hypothesis for the prediction of toxicological properties:
"The members of this category [...] are all substances which are based on a perylenetetracarboxyl group as common structural moiety. These chemicals can be included in a single category for several reasons. All substances have a similar chemical structure and exhibit physico-chemical properties in a very comparable range. They are neither soluble in water nor soluble in organic solvents, which results in a very low bioavailability. The substances in this category do not possess any properties indicating a hazard for human health. All substances are expected to be inert and not prone to transformation. The different substituents in the perylene moiety do not lead to substantial alterations in the physico-chemical and human toxicological properties of the substances".

ECHA understands from this hypothesis that you base your predictions on the assumption that different compounds have similar toxicological properties as a result of structural similarity and similar physio-chemical properties. As an integral part of this prediction, you assume absence of toxicity due to the fact that the category members have negligible bioavailablility.

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

Structural dissimilarities

Structural similarity is a prerequisite for applying the grouping and read-across approach according to REACH Annex XI, Section 1.5. As outlined in Read-Across Assessment Framework (RAAF) 2017 (March), section 3.2, in order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

In the applicability domain section of your category documentation you identified elements of structural similarity among the category members as well as structural differences, namely allowed different perylene tetracarboxyl substituents. You have not, however, provided any considerations on these structural differences and in particular on the potential impact of these structural differences on toxic properties.

Thereby, ECHA concludes that you have not addressed the obvious structural differences between the source substances and the target substance and did not explain why those differences would not lead to differences in the toxicity profile of target and source.
In your comments to the initial draft decision, you informed that you are planning to perform experimental studies with appropriate category members, aiming at further strengthening the category approach.

Lack of data to support the read-across hypothesis

According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008) *"a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved"*.

In your original read-across hypothesis attached to the dossier, you state that the category members have low solubility in water and organic solvents, which results in a very low bioavailability, and that they are expected to be inert and not prone to transformation.

You have not submitted any data to support the claim of low bioavailability, inertness or no biotransformation, or any claim on the link between such properties and low solubility.

ECHA considers that your claims on low bioavailability, based on low solubility in water and organic solvents, and on inertness not prone to biotransformation are not substantiated by biological data relevant for humans.

ECHA therefore concludes that your read-across hypothesis is not supported by sufficient information. Consequently, this hypothesis can not be verified nor accepted as basis of any reliable predictions.

In your comments to the initial draft decision you presented your intention to perform static and dynamic dissolution assays to support the claims of poor absorption and low bioavailability. ECHA will evaluate your information after the deadline of this decision, according to the specific rules of column 2 adaptations in Annex IX, sections 8.6.2. and 8.7.2, last indent, and in support of an adaptation according to Annex XI, section 1.5.
In the updated category justification included in your comments, there is no claim of inertness or no biotransformation.

Data density to derive a regular toxicological pattern

A number of factors contribute to the robustness of a category. According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.1.5., (version 1.0, May 2008), one of these factors is the density and distribution of the available data across the category. In order 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.

You claim that "*In summary, the pigments of this category are of low acute toxicity, not irritating to skin and eyes, not sensitizing and not genotoxic. The risk even after repeated exposure is considered very low and they do not pose a hazard to reproduction and development*" for the category member substances. ECHA has made the following observations:

1. As regards genotoxicity, 5 of the 9 included category members (Pigment red 224, Pigment red 178, Pigment red 149, Pigment red 179 and Pigment black 32) were tested only in a bacterial reverse mutation assay. In addition, 3 out of the 9 included category members (Pigment black 31, Perylene black I and Perylene black II) were also tested in *in vitro* test for mammalian chromosomal aberrations or *in vivo in a* micronucleus study. Two out of 9 included category members (Pigment violet 29 and Perylene black I) were tested in a bacterial reverse mutation assay and in an *in vitro* test for mammalian gene mutation.

   ECHA notes you did not explain why the tested substances are representative of the other category members with regard to genetic toxicity properties.

2. As regards repeated dose toxicity, 5 out of 9 included category members (Pigment violet 29, Pigment red 224, Pigment red 178, Pigment red 179 and Pigment black 32) do not have data provided on oral toxicity. Three category members (Pigment black 31, Perylene black I and Perylene black II) have been tested by an oral short-term (28-day) (OECD 407) toxicity study and one of the category members (Pigment red 149) by an oral sub-chronic (90-day) study. Furthermore, no repeated dose toxicity studies by the inhalation route have been provided.

   ECHA notes you did not explain why the tested substances are representative of the other category members with regard to repeated dose toxicity.

3. As regards reproductive toxicity, a reproductive/developmental toxicity screening test (OECD 421) is available for 2 of the 9 included category members (Pigment violet 29 and Perylene black I). Furthermore, no pre-natal developmental toxicity studies have been provided.

   ECHA notes you did not explain why the tested substances are representative of the other category members with regard to reproductive toxicity.

Considering the revised applicability domain of the category and the distinct structural differences between the members of the category, ECHA notes that there are too few data points (i.e. low data density) in the current data matrix for demonstrating consistent trend(s) and making the suggested predictions for the listed toxicological endpoints.
In your comments to the initial draft decision, you presented your intentions to perform toxicological tests *"[...] the most appropriate and representative substances of the category shall be used to perform additional studies. For instance, several new toxicity studies including but not limited to pre-natal developmental toxicity and 90-day repeated dose toxicity will be performed"*. ECHA notes your intentions for your testing strategy for the category. ECHA notes that it is your responsibility to fufil the requested information requirements. You also indicate that you believe that performing every single study for all category members evaluated is not scientifically justified and contradicts the REACH animal welfare concept.

As stated above, based on the assessment of the submission for the initial draft decision, there are currently too few data points (i.e. low data density) in the current data matrix for demonstrating consistent trend(s) and making the suggested predictions for the listed toxicological endpoints. Hence, this current approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA will evaluate your information after the deadline of this decision.

Conclusion

Overall, ECHA considers that the currently provided supporting data do not establish a scientifically credible link between structural similarity and the predicted toxicological endpoints, and is not sufficient to predict human health properties of the registered substance.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

While the current read-across adaptations are rejected, it is in your discretion to improve the provided adaptations under your own responsibility. ECHA notes that read-across adaptations for sub-chronic toxicity and reproductive toxicity would require, in addition to an adequate study for the endpoint with a source substance, further supporting information (*e.g.*, a

combined repeated dose toxicity study with the reproductive/developmental toxicity screening test on the target substance). ECHA notes that, for read-across adaptations, it is critical to demonstrate that the structural differences of the target and source substance will not have an impact on the toxicity and that the human health effects can indeed be predicted from the data for the source substance.

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 as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for *in vitro* chromosome aberration tests (OECD TG 473) with the analogue substances Pigment Black 31 (EC no 266-564-7), Perylen Black I (EC no 479-300-2) and Perylen Black II (EC no 475-310-6).

In your comments to the initial draft decision, you explain that a report of the US EPA concluded that "C.I. Pigment Violet 29 is unlikely to be a carcinogen". However, this statement cannot be considered as evidence of absence of cytogenicity of the registered substance (Annex VIII, Section 8.4.2).

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier contains negative results for the Annex VII, Section 8.4.1. information requirement. The registration dossier does not contain an appropriate study record for the Annex VIII, Section 8.4.2. information requirement (see section 1 above). Adequate information on in vitro gene mutation in mammalian cells will however need to be

present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under 1. has negative results.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for *in vitro* gene mutation studies in mammalian cells (OECD TG 476) with the analogue substances perylene-3,4:9,10-tetracarboxydiimide (EC no 201-344-6) and Perylen Black I (EC no 479-300-2).

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected.

In your comments to the initial draft decision, you explain that a report of the US EPA concluded that "C.I. Pigment Violet 29 is unlikely to be a carcinogen". However, this statement cannot be considered as evidence of absence of cytogenicity of the registered substance (Annex VIII, Section 8.4.2).

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1. has negative results.
ECHA set the deadline for provision of the information to allow for sequential testing.

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for "Reproductive/ developmental toxicity screening test" (OECD TG 421) with the analogue substances perylene-3,4:9,10-tetracarboxydiimide (EC no 201-344-6) and Perylen Black I (EC no 479-300-2).

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid dust, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

4. 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 as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a "sub-chronic toxicity study (90-day)", oral route (OECD TG 408), with the analogue substance Pigment Red 149 (EC no 225-590-9). In addition, study records for "short-term repeated dose toxicity studies (28-day)", oral route (OECD TG 407) with the analogue substances Pigment Black 31 (EC no 266-564-7), Perylen Black I (EC no 479-300-2) and Perylen Black II (EC no 475-310-6) were included.

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected. Furthermore, ECHA notes that the "short-term repeated dose toxicity study (28-day)" does not provide the information required by Annex IX, Section 8.6.2., because exposure duration

is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. The information provided in the technical dossier and the chemical safety report on properties of the registered substance and its uses (including for example [redacted]) indicate that human exposure to the registered 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] Furthermore, the substance is respirable [redacted] of low water solubility and consequently there is a potential for accumulation of the substance in the lungs. In the dossier you indicate that the main potential hazards are likely to be related to inhalation exposure (*"The main hazard results if dusty material is inhaled at doses at which the natural clearance function of the lung is overloaded"*).

In your comments to the initial draft decision, you explained that you consider the oral route as more appropriate than inhalation for better comparison of existing and new study data, and since you consider human exposure by inhalation as very unlikely in industrial or professional settings. More specifically, you explain that inhalation is unlikely due to technical containment or the use of personal protection equipment. For consumers you assume that exposure might be possible through attrition processes but the released particles are firmly embedded within matrix material particles.

The information provided in the Exposure Scenarios of the Chemical Safety Report attached to your comments includes, however, several industrial, professional and consumer uses for which human inhalation exposure is likely. The registered substance is used in consumer products as a colouring agent in paints, coatings and inks. The uses, e.g. PROCs 7 and 11 (industrial and non-industrial spraying), PROC 5 (mixing and blending), PROC 24 (high mechanical energy work-up of substance bound in materials and on articles e.g. sanding) and PROC 28 (manual maintenance of machinery, repair and cleaning tasks) indicate that human exposure to the substance by the inhalation route is likely.

You also indicate in the [redacted], attached to your comments, that based on health surveillance examinations, adverse health effects suspected to be related to several pigment exposure have not been observed among workers. nECHA notes that although no adverse health effects have been observed, this information does not show proof of lack of inhalation exposure.

Therefore, ECHA considers that the inhalation route is more appropriate than the oral route.

In your comments to the initial draft decision, you indicate that if the 90-day inhalation study remains as a request, you suggest performing FRAS and alveolar macrophage activity assays to investigate the induction of oxidatative stress due to surface reactive properties. In addition, you indicate that short-term inhalation tests (5-day inhalation exposure with 21

days recovery group) with representatives of the perylene-based pigments category can be considered as you see that a short-term inhalation test is regarded as better suited to investigate this substance property.

The duration of a short term inhalation study is not comparable to a sub-chronic 90-day study and it does not give the same information as a long-term study does (e.g. histopathology and clinical chemistry parameters).

ECHA reminds that the revised OECD TG 413 (adopted 25 June 2018) accommodates the testing of solid aerosols and recommends measurements of lung burden when a range-finding and/or main study or other relevant information suggests that a solid aerosol is poorly soluble and likely to be retained in the lung; hence, avoiding the risk of artificial lung-overload effects.

ECHA considers it is your responsibility if you wish to undertake additional studies in order to support an adapatation for the current request.

Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

There is evidence that the lower respiratory tract is a site of deposition and retention of the registered substance because the substance 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. The measurements shall therefore be conducted as described in the guideline version adopted on 25 June 2018.

According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats inhalation route (test method: OECD TG 413). 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 test guideline.

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

In the technical dossier, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for "Reproductive/ developmental toxicity screening tests" (OECD TG 421) with the analogue substances

perylene-3,4:9,10-tetracarboxydiimide (EC no 201-344-6) and Perylen Black I (EC no 479-300-2).

However, as explained above in Appendix 1, section Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected.

In addition, ECHA notes that the "Reproductive/ developmental toxicity screening test" does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations.

Furthermore, you have sought to adapt this information requirement according to Annex IX, Section 8.7., column 2. You provided the following justification for the adaptation: " *In accordance with Annex IX (8.7) of the REACH legislation, the reproductive toxicity studies do not need to be conducted if the substance is of low toxicity and there is no evidence of absorption from a toxicokinetic study and there is no significant human exposure. Lack of toxicity and therefore indirectly absorption were shown experimentally and are also supported by the physico-chemical properties of the test article. In two Reproduction / Developmental Toxicity Screening Tests (OECD 421) with two category members (see attached CSR for category justification), no toxicological relevant effects were reported up to the highest dose tested (1000 mg/kg). In addition, no relevant findings were reported for pups; they neither exhibited any malformations nor showed alterations in body weight, sex ratio or organ development (macroscopically). In addition, several members of the category were tested in repeated dose toxicity studies (28d and 90d) and no toxic effects were reported up to the highest dose levels tested, further demonstrating the overall low toxicity profile and the lack of absorbance of this substance class. Taken together, the physico-chemical characteristics and the available repeated dose toxicity data strongly indicate that the substance is not systemically available. There is no significant human exposure because the substance is handled at an inhalable dust only by industry specialized for handling of dusts. The pigment is incorporated into coatings at low concentrations so that there is no significant exposure of the general population."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX; Section 8.7., column 2. This adaptation requires that:

i. the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available),
ii. it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air)
iii. and there is no or no significant human exposure.

ECHA observes that those criteria are not fulfilled. More specifically:

i. Your claim of low toxicity is based on read-across information that is not accepted (see Appendix 1, section "Grouping of substances and read-across approach" of this decision);
ii. the dossier does not contain any toxicokinetic study or other proof from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure, and
iii. according to the use and exposure information included in the dossier, the

substance does have widespread industrial, professional and consumer uses, including widespread dispersive indoor/outdoor use,spraying applications and abrasion, that can result in (significant) human exposure, which contradicts the statement of no or no significant human exposure.

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, Section 8.7.2.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a dust, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

ECHA notes you have provided comments which outline the synthesis and tonnage of perylene based pigments. The information on tonnages does not affect this specific substance in the category.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 24 July 2018.

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 requests.

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 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.