

Helsinki, 8 November 2019

Addressee: [REDACTED]

Decision number: CCH-D-2114488744-33-01/F

Substance name: 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 number: 266-564-7

CAS number: 67075-37-0

Registration number: [REDACTED]

Submission number: [REDACTED]

Submission date: 15/04/2013

Registered tonnage band: 10-100

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 gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**
- 2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421) in rats, 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>.

Authorised¹ 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 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII 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* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.); and
- screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.).

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']diiisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 266-564-7)
- [7] *Pigment black 32*: 2,9-bis(p-methoxybenzyl)anthra[2,1,9-def:6,5,10-d'e'f']diiisoquinoline-1,3,8,10(2h,9h)-tetrone (EC No 280-472-4)

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

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

[9] *Perylene black II:* [REDACTED]
[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 bioavailability.

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 fulfil 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 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.

ECHA will evaluate the revised category justification including the choice of test substance(s), the indicated information to demonstrate low bioavailability and the provided toxicological studies only after deadline of this decision.

1. 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.

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).

2. 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.

Hence, 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.

You provided a sub-acute toxicity study with the registered substance. Hence, a reproductive/developmental toxicity screening test according to OECD TG 421 is appropriate.

According to the test methods OECD TG 421, 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) 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).

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 carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

Furthermore, 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.