EUROPEAN CHEMICALS AGENCY

Helsinki, 21 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
07/09/2015

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Calcium bis[4-[[1-[[(2-methylphenyl)amino]carbonyl]-2-oxopropyl]azo]-3-nitrobenzenesulphonate]
EC number: 235-558-6
CAS number: 12286-66-7

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 ***28 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. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) with the Substance

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 requested information

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.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on general considerations

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 following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

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

Description of the grouping

In your registration dossier you have formed a group (category) of 'Metal Laked Mono-Azo Yellow (ONAPSA-derived) Pigments'. You have provided a read-across justification document in IUCLID Section 13 and in the CSR.

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

PY61/Pigment Yellow 61 Benzenesulfonic acid, 3-nitro-4-[2-[2-oxo-1-[(phenylamino)-carbonyl]propyl]diazenyl]-, calcium salt (2:1) EC 235-557-0

PY62/Pigment Yellow 62 Benzenesulfonic acid, 4-[[1-[[(2-methylphenyl)amino]-carbonyl]-2- oxopropyl]azo]-3-nitro-,calcium salt (2:1) EC 235-558-6

PY168/Pigment Yellow 168 Benzenesulfonic acid, 4-[[1-[[(2-chlorophenyl)amino]carbonyl]-2-oxopropyl]azo]-3-nitro-,calcium salt (2:1) EC 276-057-2

You provide the following reasoning for the grouping the substances: *"the only difference between the three substances of the group is a methyl or chloro substituent at one location on the acetoacetanilide portion."*

You define the the structural basis for the grouping as "*...salts of a divalent metal cation (Ca^{2+}) and a mono-valent organic cation based on ortho-nitroaniline-para-sulfonic acid azo linked to an acetoacetanilide derivative*" , in addition to the above reasoning for grouping. ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

You provided an updated read-across justification document, toxicokinetic assessment document, and a IUCLID dossier file attached in your comments to the draft decision. ECHA has considered them during the decision-making of this decision.

B. Predictions for toxicological properties

You have provided the following reasoning for the prediction of toxicological properties: "*The hypothesis for read across is that the only difference between the three substances of the group is a methyl- or chloro-substituent at one location on the acetoacetanilide portion, which would have a negligible influence on the hazard profile.* [...] *Metal laked pigments are of low solubility in water and octanol. As regarding to the log Kow the substances are not lipophilic, uptake via micelles with bile acids is also unlikely.*" You further consider based on theoretical (absence of) metabolism that, "*should an aromatic amine become released, the toxicity profile is dominated by the amine function, and there is comparatively little influence of a non-polar substituent in the o-position (noting the toluidine is the most hazardous variant)*".

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

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

1. *In vitro* gene mutation study in bacteria (equivalent to OECD TG 471, 1997) with the analogue substances PY 168, EC 276-057-2
2. *In vitro* gene mutation study in mammalian cells (equivalent to OECD TG 476, 1997) with the analogue substance PY 168, EC 276-057-2
3. *In vivo* mammalian erythrocyte micronucleus test (equivalent to EU B.12, 1997) with the analogue substance PY168, EC 276-057-2
4. Combined repeated dose toxicity study with the reproduction (according to OECD TG 422) with the Substance PY62, EC 235-558-6

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

i. Available data contradicts the hypothesis

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. The ECHA Guidance[2] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". 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 category members. The observation of

[2]Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

differences in relevant properties among some members of a category is a warning sign. An explanation for such a difference resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.

Your read-across hypothesis is, *inter alia,* that the physico-chemical similarity between category members is a sufficient basis for predicting the properties of the Substance. There are notable differences in water solubility (PY61: 18000 µg/L; PY62: 16 µg/L, PY168: 1697 µg/L), and partition coefficient (one order of magnitude), between the three category members.

In addition, you selected PY62 as worst-case test substance based on its potential metabolites although the classification for the potential metabolite of PY168, 2-chloroaniline, is more severe by comparison with the potential metabolites of the other category members, including toluidine.

In your comments to the draft decision you submitted an updated read-across justification:

- you clarify that PY62 was selected as the source substance for the repeated dose toxicity, reproductive toxicity and developmental toxicity because of the impurity profile raising the most hazard concern, and in case of metabolic activity would result in release of "*the most hazardous variant*", toluidine.
- you note PY 62 and 168 "*have structural alerts for mutagenicity and carcinogenicity and serve therefore as suitable example substances.*"
- you state that "*as regarding to the log Kow the substances are not lipophilic, uptake via micelles with bile acids is also unlikely.*"
- you state state "*the impurity profile of Pigment Yellow 168 and Pigment Yellow 62, the amount of aromatic amines, i.e. o-toluidine, nitro-aniline and chloro-aniline is below 1% or below the detection limit, respectively.*"

ECHA notes your comments on the impurities and structural alerts, and considers them inconclusive as the toxic properties of the main constituents have not been demonstrated to be similar or following a certain trend.

There are, however, significant differences in e.g. water solubility and partition coefficient across the category members. These significant differences may impact the (oral) bioavailability in (non-/)animal studies and therefore the prediction of hazardous properties.

Regarding your comment on logKow and uptake of the Substance after oral administration, this allegation is not substantiated and and must be rejected.

The 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.

You have not explained the impact of significant differences in e.g. water solubility and partition coefficient across the category members in relation to your prediction of hazardous properties. Instead, your interpretation of the available data focuses e.g. on molecular weight differences between the category members (<9%) to allow the identification of worst case reference substances, as well as theoretical considerations of potential metabolites and their hazard profile.

Further, these significant differences may impact the (oral) bioavailability in (non-/)animal studies and therefore the prediction of hazardous properties.

In addition, the self-classification of potential metabolites of PY168 contradicts your choice of PY62 as worst-case test substance.

These elements are in disagreement with your conclusion on similar properties as a basis to predict, as well as your choice of worst-case substances for the relevant tests. The available data do not support, but instead contradict your hypothesis that the differences between category members *"have a negligible influence on the hazard profile."*

ii. 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).

To prove your hypothesis *"adequate and reliable documentation"* must include
a. information to substantiate absence of metabolites, and
b. bridging studies to compare properties of the category members.

a. Missing supporting information to substantiate the absence of metabolites

As indicated above, your read-across hypothesis is based on the assumption that the source substance do not metabolise into classified metabolites (e.g. toluidine, aniline). In this context, relevant, reliable and adequate information on metabolism (e.g., toxicokinetic studies) is necessary to confirm the absence of formation of the identified metabolites.

You have provided an OECD TG 422 with PY62, which exhibits no effects above the limit dose of 1000 mg/kg bw/d. To substantiate your allegation about absence of metabolites cited at the beginning of section **B.** above, no reliable information on the absence of metabolites after an exposure duration relevant for the adapted information requirements (e.g. 90 days) is available.

In your comments to the draft decision

- you consider formation of methyl-aniline or chloro-aniline by cleave unlikely because *"amide bonds are chemically stable and require extreme pH level and temperatures above 100°C to be hydrolysed."*
- you claim *"the toxicity profile is dominated by the amine function, and there is comparatively little influence of a non-polar substituent in the o-position (noting the toluidine is the most hazardous variant)"* and point out the potential metabolites after azo-bond cleavage. You did not provide the related supporting data (e.g. robust study summaries of the relevant studies) in your documentation.
- you cross-refer to available static and dynamic dissolution assays with analogue substance outside the scope of your category (EC 600-736-8) to support the claims of poor absorption and low bioavailability. You did not provide ECHA with the related data (e.g. robust study summaries with results, conclusions and test material characterisation) and explain the relevance of the indicated supporting information to Metal Laked Mono-Azo Yellow (ONAPSA-derived) Pigments in your documentation in your documentation.

[3] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

ECHA notes that enzymatic cleavage (i.e. hydrolysis) of amide bonds may occur in living organism which do not require extreme pH and temperatures to be hydrolysed.

The provided information gives merely indications instead of demonstrating an absence of potential metabolites. You have not provided reliable information on the metabolism of the substances including the identification of all metabolites (e.g. toxicokinetic studies).

The same applies to the information provided in your comments in the absence of any substantiation to your allegation on the cleavage of the amide bond. ECHA is not able to conduct an evaluation of the indicated supporting information at this stage in absence of complete documentation.

Further, future data cannot be taken into account for assessing a read-across adaptation under compliance check.

Therefore, you have not provided sufficient supporting information to strengthen the rationale for the read-across.

b. Missing supporting info/bridging studies to compare properties

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.

One category member has been tested per each of the endpoints listed at the beginning of section B. No information is available for the other two category members for that given endpoint.

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.

You did not provide valid and appropriate (bridging) studies to compare the properties of all category members with regard to genotoxicity, repeated dose and reproductive/developmental toxicity.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties.

Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In the absence of such supporting information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the target substance. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

C. Conclusions on the read-across approach

As explained above, your adaptation does not currently comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is it is rejected and it is necessary to perform testing on your Substance.

In your comments to the draft decision you indicate your intention to develop a "testing strategy to strengthen the category approach" in dialogue with ECHA. Only comments submitted to the draft decision during the decision-making procedure will be considered. ECHA will evaluate your information after the deadline of this decision, according to the specific rules of an adaptation according to Annex XI, section 1.5.

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

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

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. supporting in vitro gene mutation study in bacteria with the Substance.
ii. key in vitro gene mutation study in bacteria (according to OECD TG 471, with Prival modification) with an analogue substance (pigment yellow 168)

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

No study provided that meets the standard information requirement

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 supporting study with the Substance you have provided was not conducted with:
a) the Prival modification, in spite of the fact that the tested substance is an azo-dye/a diazo-compound.
b) 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, which you recognised for the supporting study by identifying it as unreliable.

Annex XI adaptation not met

Moreover, you have adapted the standard information requirement according to Annex XI, Section 1.5. Grouping of substances and read-across approach by providing a study record for an in vitro gene mutation study in bacteria.

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

In your comments to the draft decision you indicate your agreement to conduct the requested study.

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

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

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

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

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

In your comments on the draft decision you consider that the request of the study is unjustified since valid read-across data is vailable, and that "*an updated read-across justification according to the requirements of the read across assessment framework will be submited.*" However, as explained in the Appendix General consideration, your adaptation according to Annex XI, Section 1.5 is for the moment rejected. Your updated dossier will be evaluated after the deadline of this decision.

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

2. **Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);**

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

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

In your comments on the draft decision you consider that the request of the study is unjustified since valid read-across data is vailable, and that "*an updated read-across justification according to the requirements of the read across assessment framework will be submited.*" However, as explained in the Appendix General consideration, your adaptation according to Annex XI, Section 1.5 is for the moment rejected. Your updated dossier will be evaluated after the deadline of this decision.

Your dossier contains insufficient data for an *in vitro* gene mutation study in bacteria (section 1 of Appendix A), and an adaptation for an *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study which are rejected for the reasons provided in section 1 of Appendix A and in the Appendix General considerations.

The result of the requests for information in section 1 of Appendix A and in section 1 of this Appendix B will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

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.

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 low solubility, no absorption, and no systemic effects observed in a study according to OECD TG 422.

We have assessed this information and identified the following issues:

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 criteria, including:

(i) the Substance is not inhalable and
(ii) there is no evidence of absorption,
(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 your Substance is inhalable (as discussed further below) and uses are reported that include spray application.

In your comments on the initial draft decision you explained that "*As the substance is a powder, inhalation of particles is feasible. However, only* [redacted] *of the test material as such includes particles of inhalable size*". Furthermore you wrote "*The test item is a solid with a small fraction of inhalable particle size. Though, as shown in chapter 3 of the IUCLID file, the substance is handled as* [redacted] *The (unformulated) powder form of the is restricted to the production site and handled by well trained worker*". For the granulometry you describe that the MMD is [redacted] and D10 is [redacted]. In addition, as an attachment to your comments, you provided exposure scenarios and risk characterisation calculations for the uses of the Substance. Many of the provided ESs have conditions of use that create dust or aerosol e.g. spraying (PROC 11), rolling application and brushing (PROC 10) and low or high energy manipulation of substances bound in/on materials or articles (PROC 21 and 24). Therefore, the Substance is inhalable.

(ii) You did not provide information demonstrating that there is no evidence of absorption. You indicated that a discoloration of faeces indicates that the substance will be excreted unchanged. This provide inconclusive information and cannot be considered as no evidence of absorption.

In your comments to the initial draft decision, and in an attachment to the comments, you refer to acute toxicity studies and to a screening study performed with an analogue substance according to OECD TG 422. You explain that "*Due to its high molecular weight* [redacted] *gastrointestinal and dermal absorption is expected to be very*

limited. Furthermore, yellowish discoloration of the feces was observed in several studies, indicating that the substance is excreted unchanged". The provided information does not conclusively support your argument and does therefore not demonstrate that there is no evidence of absorption.

(iii) Human exposure cannot be considered as limited because widespread uses, including professional and consumer uses are reported.

In your comments on the initial draft decision you included exposure scanarios and exposure level estimations. You also predict notable exposures via inhalation in many mixing and transferring tasks (PROCs 5, 8a and 8b). Your data presents for professional users inhalation exposure concentrations as high as 9.6 mg/m^3 (PROC 10) and 8.2 mg/m^3 (PROC 11)

Due to the granulometry, the registered substance is inhalable and the predicted exposure levels presented for your exposure scenarios do not describe "limited human exposure".

Therefore, your adaptation is rejected.

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

In your comments on the initial draft decision you state "*Since the conditions for waiving defined by EC regulation 1907/2008, Annex IX, 8.6.2 are fulfilled and a sub-chronic toxicity study is not expected to add any further relevant knowledge on this endpoint and due to animal welfare aspects and/or laws, an additional study is therefore not warranted".* ECHA disagrees with your statement because, as presented above, all criteria of Annex IX, Section 8.6.2, column 2, are not fulfilled and your adaptation is not accepted.

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the inhalation route is the most appropriate route of administration to investigate repeated dose toxicity[4] 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 (industrial, professional and consumer uses, including PROC 11 non-industrial spraying) indicate that human exposure to the Substance by the inhalation route is likely. More specifically, the Substance is reported to occur as a dust with a significant proportion of particles of inhalable size. Furthermore, the Substance is respirable (D10 [redacted]), of low water solubility and 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.

In your comments on the initial draft decision you explain that you are planning to perform tests according to a tiered approach, starting with in vitro bioelution tests, followed by short term inhalation test and finally 90-day study(ies) (*"Single pigments representing a toxicological category ("insoluble and no toxicity" or "insoluble and local effects" etc.) are then tested to examine their toxicological properties after sub-chronic exposure"*. ECHA notes that

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

you are free to perform additional tests or to include adaptations in your dossier. Future data cannot, however, be taken into account at this stage.

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 no bioavailability and no systemic effects observed in a study according to OECD TG 422.

We have assessed this information and identified the following issues:

Annex IX column 2 adaptation not met

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, two of them being:

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

You have not demonstrated that those criteria are met:

(i) You have not provided any toxicokinetic data to prove that no systemic absorption occurs. The OECD TG 422 study provided did not investigate toxicokinetic properties such as absorption.
(ii) Furthermore, as discussed under section 1 of Appendix C, the reported uses of the Substance indicate that there is possibility of significant human exposure.

Therefore, your adaptation is rejected.

OECD TG 422 study does not fulfill the requirement

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, 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 a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422). In this study, structural malformations and variations are not investigated as required in the PNDT study (OECD TG 414). Therefore, this study 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 oral[5] administration of the Substance.

In your comments on the initial draft decision you agree to perform the requested study.

[5] 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 14 January 2019.

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

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

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'[6].

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 and other parameters relevant for the property to be tested. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[7].

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

5. List of references of the ECHA Guidance and other guidance/ reference documents[8]

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)[9]

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

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

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

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

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

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

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

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

OECD Guidance documents[10]
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.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] 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 fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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