EUROPEAN CHEMICALS AGENCY

Helsinki, 26 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359364-45-01/F
Substance name: COPPER, [29H,31H-PHTHALOCYANINATO(2-)-N29,N30,N31,N32]-, [[3-(DIMETHYLAMINO)PROPYL]AMINO]SULFONYL DERIVS.
EC number: 270-096-9
CAS number: 68411-04-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22.09.2014
Registered tonnage band: 100-1000T

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. **Composition (Annex VI, Section 2.3.) of the registered substance;**
2. **Description of the analytical methods (Annex VI, Section 2.3.7.);**
3. **Granulometry (Annex VII, Section 7.14.) of the registered substance;**
4. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**
5. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422 in rats, oral route with the registered substance;**
6. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
7. **Identification of degradation products (Annex IX, 9.2.3.; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25./OECD TG 309) at a temperature of 20 °C with the registered substance**.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation. **4 November 2019**. 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. 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, shall 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 Kevin Pollard, Head of Unit, Evaluation E1

[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

IDENTIFICATION OF THE SUBSTANCE

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

1. Composition of the substance (Annex VI, Section 2.3.)

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations.

Annex VI, Section 2.3. of the REACH Regulation requires that each registration dossier contains sufficient information for establishing the composition of the registered substance and therefore its identity.

In that respect according to chapter 4.3 of the 'Guidance for identification and naming of substances under REACH and CLP' (June 2016, Version 1.4), referred thereafter as the Guidance, for UVCB substances, the following applies:

- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually,
- All known constituents and constituents relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually; and
- Other constituents shall be identified as far as possible by a generic description of their chemical nature.
- For each constituent or group of constituents, the typical, minimum and maximum concentration levels shall be specified.

ECHA notes that in section 1.2 of the IUCLID dossier you have reported the composition as consisting of [redacted]% of the generic reference substance "[redacted]" without providing any information on the identity and concentration levels of the constituents or groups of constituents present in the composition. However ECHA notes further that in contradiction the analytical report "[redacted]" included in section 1.4 of the IUCLID dossier contains information indicating the presence of several constituents/group of constituents (see Fig. 8 and 9 in the mentioned file).

As explained above, all constituents identified in the analytical report included in section 1.4 should be reported individually in section 1.2. Because of the missing reporting of the different constituents/group of constituents in section 1.2 your registration does not contain consistent information for establishing the composition of the registered substance and therefore its identity. ECHA therefore concludes that the compositional information has not been provided to the level of detail required by the Guidance as described above.

You are accordingly requested to revise the information on the composition of the registered substance in order to establish a precise chemical representation of what the substance consists of. For your substance apparently consisting of different groups of constituents (i.e. isomers), we expect as compositional information the reporting of the different constituents separately with a representative typical concentration and concentration range values.

For each constituent required to be reported individually, the IUPAC name, CAS name and CAS number (if available), molecular and structural formula, as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID.

For the other constituents to be reported under a generic description, a generic chemical name describing the group of constituents, generic molecular and structural information (if applicable), as well as the minimum, maximum and typical concentration, shall be reported in the appropriate fields in IUCLID.

Further technical details on how to report the composition of substances in IUCLID are available in the Manual "How to prepare registration and PPORD dossiers" on the ECHA website. Information on how to report several compositions in IUCLID is specified in paragraph 2.3, Q&A8 of that manual.

You shall also ensure that the composition is verifiable and therefore supported by analytical data and a description of the analytical methods used for the identification and quantification of the constituents required to be reported, as required under Annex VI, Section 2.3.7.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have agreed with the information requirements in the draft decision. In addition, you have indicated your intention to revise Section 1.2 of your IUCLID dossier addressing the information requirement in an update of the registration. ECHA will examine such information only after the deadline set in the adopted decision has passed and all the substance information requested in this decision has been submitted.

2. Description of the analytical methods (Annex VI, Section 2.3.7.)

Annex VI, section 2.3.7 of the REACH Regulation requires that each registration dossier contains a sufficiently detailed description of the analytical method used for establishing the composition of the registered substance and therefore its identity. This information shall be sufficient to allow the method to be reproduced.

In IUCLID section 1.4 you have reported a description of a HPLC-MS analysis for qualitative and quantitative determination of the constituents. However, ECHA notes that in such analysis the peaks are not efficiently separated, a peak list is missing and not all the peaks are identified. With the current analytical report it is not possible to get a clear understanding of the quantification of the different constituents/groups of constituents of the registered substance.

Such data cannot be obtained either from the compositional information provided in IUCLID section 1.2, because (as described in the previous point) only a generic constituent has been recorded.

Consequently, ECHA concludes that you did not provide sufficient description of the analytical methods used for the identification and quantification of the constituents/groups of constituents required to be reported in the composition of the registered substance.

In line with Annex VI Section 2.3.7 you are accordingly requested to provide a description of the analytical methods used for the identification and quantification of the constituents or groups of constituents required to be reported in the composition of the registered substance. The description shall be sufficient for the methods to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

You should note that ECHA will consider any method that is suitable to verify the composition, including any indirect method involving chemical derivatisation of the substance or any analysis involving also considerations on the starting materials and the manufacturing process.

As for the reporting of the data in the registration dossier, the information shall be attached in IUCLID section 1.4. You shall ensure that the composition reported in the dossier according to Annex VI section 2.3 is consistent with the analytical results obtained.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you have agreed with the information requirements in the draft decision. In addition, you have indicated your intention to revise the Section 1.4 of your IUCLID dossier addressing the information requirement in an update by undertaking additional analytical attempts to better resolve the compositional information of the constituents in IUCLID section 1.2. ECHA will examine such information only after the deadline set in the adopted decision has passed and all the substance information requested in this decision has been submitted.

PROPERTIES OF THE SUBSTANCE

Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for sub-acute toxicity (Annex IX, Section 8.6.1.) and screening for reproductive toxicity (Annex VIII, Section 8.7.1) by applying a read-across adaptation following REACH Annex XI, Section 1.5.

You are using this read-across adaptation as an element to adapt further the standard information requirements for

- Repeated dose toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

With respect to specific column 2 adaptations on low toxicity, please see the respective sections below.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and a property-specific context.

Description of the grouping and read-across approach proposed by the Registrant

You have provided the following arguments to justify the read-across approach:

- *"Both substances are blue colored solid powders. The plane aromatic structure, with a central copper atom give the molecules an exceptional high stability. Both molecules have a nearly identical structure with the minor exception of a terminal methylethoxy group (Orasol Blue 825) instead of a dimethylamino group (C.I. Direct Blue 264) in the sulfonylaminopropyl side chains."*
- *"Due to the similar chemical structure of **C.I. Direct Blue 264** and **Orasol Blue 825** a read-across between both compounds was initially suggested and experimentally verified. Toxicological investigations indicate that both compounds are not bioavailable and, consequently, not toxic even at the limit dose of 1000 mg/kg bw/day in repeated dose toxicity experiments. Based on the blue color of the substances, a coloration of feces and potential coloration of carcass, organs and urine is particularly valuable for the evaluation of bioavailability in repeated dose toxicity experiments."*
- *"Overall, from the data of these repeated dose studies, there is no evidence of a toxicological relevant absorption of **C.I. Direct Blue 264** or **Orasol Blue 825**."*
- *"In all toxicological studies, similar results were obtained with both substances and it can be concluded that both compounds are not toxic in any test. Based on the animal experiments no bioavailability is assumed for both compounds. Therefore a read-across for toxicological endpoints is justified."*

ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

Support of the grouping and read-across approach

You have provided a read-across justification as a separate attachment (Annex) in the CSR. This or similar information has also been included in the relevant endpoint summaries in the registration, both in the CSR and in the IUCLID file. In summary you provide the following arguments to support the read-across approach:

- Structural similarity between the target substance C.I. Direct Blue 264 and the analogue substance Orasol Blue 825.
- No evidence of a toxicological relevant absorption of C.I. Direct Blue 264 or Orasol Blue 825.
- Similar results were obtained with both substances in studies of acute toxicity, skin irritation/corrosion, eye irritation, genotoxicity, subacute and reproductive toxicity, and it can be concluded that both compounds are not toxic in any of these tests.

ECHA observes that you have provided the following study summary within the IUCLID endpoint 7.5.1. "repeated dose toxicity, oral" and 7.8.1. "toxicity to reproduction":

- Combined repeated dose toxicity with the reproduction/developmental toxicity screening test (OECD TG 422) by the oral route with the analogous substance Orasol Blue 825 (EC 279-767-0) ([redacted] 2013)

ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

With regard to the proposed predictions ECHA has the following observations:

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 "*How to report on Read-Across"* it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

ECHA notes the following: The target (registered) substance is a UVCB and the composition of the substance has not been described in sufficient detail (see Section 1 above). For the source substance, the major constituent accounts for [redacted]% of the substance but no information on impurity profile has been reported.

ECHA concludes that the current information does not allow a side-by-side comparison of the constituents between the source and target substances.

(ii) Explanation on why and how the structural similarities allow predictions

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.
ECHA notes the following:

a. You state that the source and target molecules have a nearly identical structure with the minor exception of a terminal methylethoxy group (Orasol Blue 825) instead of a dimethylamino group (C.I. Direct Blue 264) in the sulfonylaminopropyl side chains. However, the possible implications of this structural difference in terms of physicochemical or toxicological characteristics are not further explained or discussed in your read-across justification.

b. You state that both the target and the analogue substance have exceptionally high stability. There is, however, no factual evidence provided to substantiate this statement.

ECHA concludes that you have not explained why the structural difference indicated in point a. above would not lead to differences in the toxicity profile of target and source substances. Furthermore the stability of the substances upon administration has not been substantiated.

(iii) Support of a similar or regular pattern as a result of structural similarity

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.* One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

ECHA notes the following:

a. For the source substance, an OECD TG 422 screening study ([redacted] 2013) was provided with NOAELs of 1000 mg/kg bw/d for systemic toxicity and reproductive toxicity.

b. For the registered substance, a 14-day pilot (non-guideline) gavage study in 3 rats per sex and dose group ([redacted] 2012) was provided with no effects reported up to 1000 mg/kg bw/d on survival, clinical examination, body weight, food consumption, water intake and necropsy.

c. You report from both studies a lack of toxicologically significant findings.

ECHA considers that the results of these studies cannot be used to predict the similarities in toxicological profiles with respect to sub-acute toxicity and screening for reproductive toxicity, because in the 14-day pilot study performed with the registered substance, no histopathological examination was reported. Furthermore, the pilot study does not provide specific information related to reproductive toxic effects, the exposure period was only 14 days, and too few animals were tested in this study resulting in a too low statistical power of the results. Hence, it is not possible to conclude on the absence of toxicologically significant findings of the registered substance with respect to sub-acute toxicity and screening for reproductive toxicity.

ECHA concludes that the presented evidence does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore, it cannot be verified that the proposed analogue substance can be used to predict properties of the registered substance.

(iv)Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

In your read-across justification you state the following:

"*Toxicological investigations indicate that both compounds are not bioavailable*" and "*Based on the blue color of the substances, a coloration of feces and potential coloration of carcass, organs and urine is particularly valuable for the evaluation of bioavailability in repeated dose toxicity experiments.*"

Based on a 14-day study with the target substance you state the following:
"*The only finding at clinical examinations was blue feces color, which was observed for all treated animals and is due to the color of the test substance. Findings clearly related to the oral administration of the test compound were noticed at necropsy only in the intestinal tract in males starting at 100 mg/kg bw/day and in females starting at 500 mg/kg bw/day. Changes in content, blue, was observed in small intestine, cecum and large intestine. No other organ was colored.*"

"*To investigate potential uptake and excretion of the compound the color of the urine was investigated photometrically in this study. Urine has be collected during a period of about 16 hours at room temperature from all animals of the control and high dose groups near the end of the study. The color of the urine did not differ between these groups. Furthermore, photometry of urinary samples gave no evidence that the test substance was excreted with the urine. Based on the photometric urine analysis and the necropsy findings in this 14 day pilot study specifically designed to investigate potential compound uptake, distribution and excretion, no systemic absorption was observed.*"

Based on the OECD TG 422 screening study you state the following:
"*For the toxicokinetic evaluation, the colors of feces and urine are evaluated. Regarding clinical examination, no signs of general systemic toxicity were observed up to an oral dose level of 1000 mg/kg bw/day (highest applied dose). A blue discoloration of feces in females of test group 2 (300 mg/kg bw/day), as well as in males and females of test group 3 (1000 mg/kg bw/day) was observed. During necropsy blue discoloration of contents was seen only throughout the gastro-intestinal system in many animals of both sexes of the mid and high dose group and in one female of the low dose group. No systemic organ was discolored indicating that the compound is not bioavailable to systemic organs. No discoloration in the urine was reported in any animal investigated, again, indicating that the compound is not bioavailable.*"

ECHA notes the following:

a. The toxicokinetic information used to demonstrate lack of systemic uptake of the source and target compound seems to stem from the studies referred to under (III) above relying on optical detection of potentially blue-coloured organs. The sensitivity of this method has not been further described in your technical dossier or in the read-across justification. Without information about the sensitivity of the method it is not possible to conclude that no systemic uptake (i.e. uptake below a defined limit of detection) of the target and source substances occurred.

b. In addition photometric measurements of urine were used to demonstrate the lack of the source and target substances in urine. Also here no verification of the sensitivity of the method used has been provided. Thus, without information about the sensitivity of the method there is insufficient basis to conclude that systemic absorption is below a defined limit of detection and therefore to be considered of no toxicological significance or absent.

c. Furthermore, there is no quantitative information given on excretion of intact source or target substances. Only if this quantitative information is available it is possible by the means of calculating the mass balance to use excretion of intact substance as a mean to demonstrate that no systemic uptake of the source and target substances occur.

d. There is also no information about the metabolism of the source and target substances, or information that could demonstrate that the substances are not metabolised. Without such information it is not possible to conclude that the source and target substances are metabolised to the same substances, or that the substances are excreted without being metabolised.

Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties. 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. ECHA notes that in view of the issues listed above it has not been demonstrated that the source and read-across substances have the same properties or follow a similar pattern with regard to studies on repeated dose toxicity study (90-day), oral route (Annex IX, Section 8.6.2.), toxicity to reproduction (Annex VIII, Section 8.7.1), and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species. ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you did not further justify the proposed read-across.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints repeated dose toxicity, toxicity to reproduction and pre-natal developmental toxicity in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

3. Granulometry (Annex VII, Section 7.14.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Granulometry" is a standard information requirement as laid down in Annex VII, Section 7.14 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 VII, Section 7.14., column 2. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH Annex VII, the study does not need to be conducted as C.I. Direct Blue 264 is marketed or used in a non solid or granular form.*"

However, ECHA notes that the registered substance is reported to be a solid and the uses reported also seem to indicate that it is used in a solid form. In addition, ECHA also notes that there is no indication in the registration dossier that the registered substance might be manufactured and marketed or used only in granular form. Therefore, your adaptation does not meet the specific rules for adaptation of Annex VII, Section 7.14., column 2 and consequently, your adaptation of the information requirement is rejected.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation, you agreed with the information request.

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.

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: Granulometry. Guidance for determining appropriate test methods for the granulometry endpoint is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.14.3 (July 2015).

4. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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

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 not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2. Instead 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 "combined repeated dose toxicity with the reproduction/developmental toxicity screening test" (OECD TG 422) by the oral route with the analogous substance Orasol Blue 825 (EC 279-767-0) ([redacted] 2013), and a non-guideline 14 day repeated dose study by the oral route with the registered substance ([redacted] 2012). You have also sought to adapt this information requirement according to Annex IX, Section 8.6.2, Column 2, by providing the following waiver:

"According to REACH Annex IX Section 8.6.2 Column 2 a 90 day repeated dose toxicity study does not need to be conducted, if the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day limit test.

The requirement of a 28-day limit test is fulfilled by read-across with the chemical closely related substance Orasol Blue 825 (Copper, [29H,31H-phthalocyaninato(2-)-N29,N30,N31, N32]-, [[3-(1-methylethoxy)propyl]amino]sulfonyl derivs.; CAS No 81457-65-0; EC No 279-767-0), for which a study according to OECD TG 422 (Combined repeated dose toxicity study with the reproduction /developmental toxicity screening test day) is available."

"Overall, the requirements mentioned in REACH Annex IX Section 8.6.2 Column 2 are fulfilled to conclude that a 90 day repeated dose toxicity study does not need to be conducted, because …
1) … there is no evidence of absorption based on the findings of a 14 day pilot oral gavage study with C.I. Direct Blue 264.
2) … there is no evidence of absorption or toxicity in a Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test (OECD TG 422) with the chemical closely related substance Orasol Blue 825
3) … C.I. Direct Blue 264 is unreactive (LD50 > 5000 mg/kg bw, not irritating to eyes and skin, not sensitizing in a LLNA, all genotoxicity tests negative)
4) … C.I. Direct Blue 264 has a low water solubility.
5) … C.I. Direct Blue 264 is not inhalable, because it is an organic solid powder with a very low vapor pressure (1.92E-32 Pa at 25°C; calculated), which is not used in a solid or granular form."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2 for the following reasons:

- You state in your technical dossier (IUCLID Section 4.8) that the registered substance is moderately soluble (100-1000 mg/L). Thus, the criteria of insolubility of Annex IX, Section 8.6.2, Column 2, fourth indent is not fulfilled.
- As explained in Appendix 1, Section 0 of this decision, it has not been sufficiently demonstrated that there is no systemic absorption of the registered substance.
- As explained in Appendix 1, Section 0, of this decision, your read-across adaptation according to REACH Annex XI, Section 1.5 cannot be accepted. Consequently, the criterion "no evidence of toxicity in a 28-day limit test" has not been fulfilled as there is no valid 28-day limit test available for the registered substance.

Therefore, 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 has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration.

More specifically, based on the limited information provided, human inhalation exposure cannot be excluded. However, since the substance is a powder of moderate water solubility without reported local reactivity, there is no high concern for local effects in the respiratory tract following inhalation exposure that would require generation of information by the inhalation route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you propose that the first test of the proposed testing sequence should be a screening study for reproductive/developmental toxicity according OECD TG 422 in which toxicokinetic investigations are included. In case the toxicokinetic investigations demonstrate no relevant absorption of the registered substance further testing (e.g. OECD TG 408 and OECD TG 414) is not necessary since this information would allow for adaption of the information requirement according to the rules laid down in Annex IX of the REACH Regulation.

You further state that in case ECHA considers the above proposed testing sequence as inappropriate you proposes for reasons of animal welfare to amend the (draft) decision and (only) conduct a sub-chronic toxicity study (OECD TG 408) and a pre-natal developmental toxicity study (OECD TG 414).

ECHA is of the opinion that both of the testing strategies proposed by you seem plausible to fulfil the information requirements, and that the decision on which of the strategies to choose must be taken by you.

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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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

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

"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 not provided any study record of a screening for reproductive/developmental toxicity for the registered substance in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1. Instead, 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 "combined repeated dose toxicity with the reproduction/developmental toxicity screening test" (OECD TG 422) by the oral route with the analogous substance Orasol Blue 825 (EC 279-767-0) ([redacted] 2013). However, as concluded in Appendix 1, Section 0, of this decision, your read-across adaptation according to REACH Annex XI, Section 1.5 cannot be accepted.

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 and 422, the tests are 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a powder, ECHA concludes that testing should be performed by the oral route.

Please also see Section 4 above for ECHA's response to your comments on the draft decision.

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.

Note 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 4.1, October 2015).

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

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

A "pre-natal developmental toxicity study" (test method EU B.31./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. You have however sought to adapt this information requirement according to Annex IX, Section 8.7, Column 2, by providing the following waiver:

"According to REACH Annex IX Section 8.7. Column 2 a developmental toxicity study (OECD TG 414) does not need to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and there is no significant exposure. All available toxicological studies indicate, that C.I. Direct Blue 264 has a low toxicity (LD50 oral and dermal is > 5000 mg/kg bw, not irritating to eyes and skin, not sensitizing in a LLNA, all genotoxicity tests are negative and the NOAEL is >1000 mg/kg bw/day in a 14 day pilot study)."

"C.I. Direct Blue 264 is not inhalable, because it is an organic solid powder with a very low vapor pressure (1.92E-32 Pa at 25°C; calculated), which is not used in a solid or granular form. Therefore, the requirements to omit a developmental toxicity study (OECD TG 414) are fulfilled.

Additionally, based on read-across with the chemical closely related substance Orasol Blue 825 (Copper, [29H,31H-phthalocyaninato(2-)-N29,N30,N31,N32]-, [[3-(1-methylethoxy)propyl] amino]sulfonyl derivs.; CAS No 81457-65-0; EC No 279-767-0) no adverse effects on development were found in a study according to OECD TG 422 (Combined repeated dose toxicity study with the reproduction /developmental toxicity screening test). All surviving pups, all stillborn pups and those pups, which died ahead of schedule, were examined externally, eviscerated and their organs were assessed macroscopically.
No treatment related changes were noted during pup necropsy.

Based on these findings a developmental toxicity study (OECD TG 414) according to REACH Annex IX Section 8.7.2 will be waived for C.I. Direct Blue 264."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7.2., column 2, for the following reasons:

- As explained above in Appendix 1, Section 2 of this decision, you have not sufficiently demonstrated that the registered substance is of low toxicity, as there is no valid 28/day limit study available for the registered substance or any other equally relevant information to substantiate this assumption.
- Direct exposures to workers and consumers have not been calculated. Hence, it cannot be concluded that no significant exposures occur.
- As explained in Appendix 1, Section 0 of this decision, it has not been sufficiently demonstrated that there is no systemic absorption of the registered substance.

It is also concluded in Appendix 1, Section 0, of this decision, that your read-across adaptation according to REACH Annex XI, Section 1.5, which forms an important basis for your adaptation of the present information requirement, is rejected.

Therefore, 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 method EU B.31./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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a powder, ECHA concludes that testing should be performed by the oral route.

Please also see Section 4 above for ECHA's response to your comments on the draft decision.

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: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

7. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Column 2 of Section 9.2.3. of Annex IX further states that the information does not need to be provided if the substance is readily biodegradable.

ECHA observes that in the registered dossier you have concluded that the substance is not readily biodegradable. Moreover, ECHA notes that you have not provided information on the identity of degradation products in the registration dossier.

ECHA notes that information on degradation products is required for the PBT/vPvB assessment as Annex XIII of the REACH Regulation explicitly requires that PBT/vPvB properties of degradation products need to be taken into account. Information on degradation products shall also be taken into account for the exposure assessment (Annex I 5.2.4. of the REACH Regulation) and for the hazard assessment (e.g. column 2 of Annex X 9.4 and Annex X 9.5.1 of the REACH Regulation). Finally, ECHA further points out that information on degradation products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation).

In your comments to the draft decision according to Article 50(1) of the REACH Regulation you, firstly, noted that ECHA´s expression for the identification of degradation products as a standard requirement has to be reflected in the light of the Chemical Safety Assessment (CSA) performed by you and that you have concluded that further degradation testing is scientifically not necessary.

ECHA notes that Column 1 of Annexes VII to X of the REACH Regulation lists standard information required according to Articles 10 and 12 to be provided in the registration dossiers. There are specific rules for adaptation of standard information requirements listed in Column 2 of these Annexes. As noted above in this section you have concluded that the substance is not readily biodegradable. Moreover, ECHA noted that there is no information on the identity of degradation products provided by you in the registration dossier. As listed above in this section, information on degradation products is necessary for various steps of the CSA. Thus, ECHA considers that without identification and consideration of degradation products, a CSA of the substance cannot be completed and consequently, that, for the CSA of the substance, degradation products have to be identified and properly considered.

ECHA considers that the organic groups attached to the central copper phthalocyanine parent molecule could be prone to degradation, i.e. degradation products might be formed. Furthermore, copper may be either reduced or oxidised depending on the environmental conditions affecting its bioavailability significantly. Thus, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

Secondly, in your comments to the draft decision according to Article 50(1) of the REACH Regulation you noted that you do not see the necessity for performing a simulation test in surface water (with the registered substance) as you have already stated that the registered substance is P/vP based on the screening data. However, you discussed that the registered substance is neither B/vB nor T. Furthermore, you argued that a screening test performed with the registered substance is more favourable to indicate degradation than the requested degradation simulation test in surface water. You noted that it is basic knowledge "*that due to the delocalised π electrons aromatic phthalocyanine rings are highly stable and do not undergo degradation*". Moreover, you noted that if a hydroxylated molecules are formed, these would be more polar/water soluble and these molecules would not meet the B criterion as octanol-water partitioning coefficients of such hydroxylated compounds would be even lower as those of the parent substance. Also you stated that according to basic chemistry knowledge, the copper in phthalocyanines has an oxidation stage of +II. Higher oxidation stages of copper are not known. Reduction of a copper phthalocyanine is highly unlikely in an aerobic environment and only strong reducing agents would lead to a reduction of a phthalocyanine yielding a dihydrophthalocyanine, but without reducing copper.

ECHA reminds that, as noted below, the main interest of the requested testing lies on the identification of degradation products which should be further considered in the CSA of the substance. ECHA acknowledges the conclusions made by you on the PBT/vPvB assessment of the substance itself, however considers that identification of the degradation products and its consideration in the CSA is still necessary. Once the degradation products are identified, results of consideration of these in the CSA, including for the PBT/vPvB assessment, shall be provided in the registration dossier. ECHA considers that ready biodegradability tests are designed to have stringent test conditions and the positive result of such test would indicate that the chemical will undergo rapid and ultimate biodegradation under most environmental conditions. However, as noted in ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b (version 3.0, February 2016): "*A negative result in a test for ready biodegradability does not necessarily mean that the chemical will not be degraded under relevant environmental conditions and persist in the environment. A failed ready biodegradability test indicates that further testing under less stringent test conditions should be considered at the next level.*"

Thus, ECHA considers that results of the test for ready biodegradability does not prove that no degradation and no formation of degradation products is possible under relevant environmental conditions.

Furthermore, ECHA agrees with you that based on the chemical structure the substance is likely to be resistant to abiotic degradation, however you have not provided sufficient argumentation as to why biotic degradation is improbable. There are literature studies available which demonstrate that biotic degradation of aromatic structures can occur, e.g. Study of the white-rot fungal degradation of selected phthalocyanine dyes by capillary electrophoresis and liquid chromatography. A. Conneely et al. Analytica Chimica Acta 451 (2002) 259–270 or Comparison of oil composition changes due to biodegradation and physical weathering in different oils. Z. Wang, M. Fingas, et al. Journal of Chromatography A, 809 (1998) 89–107 etc.

Moreover, ECHA notes that copper compounds with oxidation states 0, +1, + 3 and +4 are known. ECHA is not aware, whether or not these copper oxidation states are relevant for the transformation of the registered substance under environmentally relevant conditions. However, such transformations cannot be disregarded without further argumentation or evidence provided.

Thirdly, in your comments to the draft decision according to Article 50(1) of the REACH Regulation you noted that do not understand the reference given to column 2 of Annex X, Section 9.4 and Annex X, Section 9.5.1 of the REACH Regulation and why effects on terrestrial organisms are suspected in the context of a surface water simulation study.

Above ECHA has listed various references from the REACH Regulation where consideration of degradation products is noted. It is for you to identify the degradation products in various compartments and investigate whether or not identified degradation products raise any concern (e.g. possessing PBT/vPvB properties or are hazardous for living organisms in various environmental compartments etc.). Moreover, ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b (version 3.0, February 2016) notes that "*when a substance is not fully mineralised, but degraded to more persistent degradation products, the environmental exposure concentrations should be determined for these products. Consequently, the safety assessment should also consider the degradation products.*" It should be noted that one of the steps of the exposure estimation is an assessment of chemical fate and pathways of the substance (or its degradation/transformation products) with the following estimation of exposure levels in the environmental compartments. Thus, identification of degradation products in various environmental compartments should be followed by the assessment of the fate and pathways of these products in the environment, including transfers from one compartment to other environmental compartments, with consideration of possible effects of these products on the organisms living in these compartments. For instance, there is a strategy for assessing the ecological risk of organometallic compounds proposed by OECD available (OECD, 09 February 2015: Guidance on selecting a strategy for assessing the ecological risk of organometallic and organic metal salt substances based on their environmental fate. Series on Testing & Assessment No. 212. ENV/JM/MONO(2015)2) which begins with the determination of the fate of organometalls in the environment, with subsequent identification of the moieties to consider for ecological risk assessment.

Regarding appropriate and suitable test method, the method will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition degradation half-life, log Kow and potential toxicity of the metabolites may be investigated. Based on the information provided in your registration dossier, ECHA notes that the registered substance is soluble in water and high potential for adsorption is not indicated. Based on quantitative exposure assessment ECHA further notes that direct and/or indirect exposure to aquatic environment is relevant.

Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is a validated standard international test laid down in the Test Methods Regulation 440/2008 and, therefore meets the requirements of Article 13(3) of the REACH Regulation. This test shall be performed to determine the nature and rates of formation and decline of transformation products to which aquatic organisms may be exposed.

ECHA considers that for the registered substance the main interest of the testing lies on the identification of degradation products. Thus, a test temperature of 20°C is more appropriate because this would result in faster degradation rate and would therefore enhance the formation of degradation products.

Therefore, pursuant to Article 41(1)(a) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Identification of the degradation products using the following test method: Aerobic mineralisation in surface water – simulation biodegradation test (test method: EU C.25. / OECD TG 309) at a temperature of 20 °C with the registered substance.

Appendix 2: Procedural history

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 28 July 2016.

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

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments but did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) 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 test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.