EUROPEAN CHEMICALS AGENCY

Helsinki, 25 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114476156-44-01/F
Substance name: Violet sodium polysulfide aluminosilicate with a SOD-type framework structure
EC number: 701-186-2
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/11/2017
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

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

1. **Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105) with the registered substance;**

2. ***In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. /OECD TG 471) with the registered substance;**

3. ***In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487) with the registered substance;**

4. ***In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490) with the registered substance, provided that both studies requested under 2. and 3. have negative results;**

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

6. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

7. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

8. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the**

registered substance;

9. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

10. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.**

You have to submit the requested information in an updated registration dossier by ***1 February 2022***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing where relevant.

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

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment

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

Appendix 1: Reasons

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

For endpoints Sub-chronic toxicity study (90-day) (Annex IX, section 8.6.2.); Screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.), Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.), in vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.), in vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.), in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.) and Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) your registration dossier contains adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach in general before the individual endpoints (sections 2 to 9).

Grouping of substances and read-across approach

You have sought to adapt the information requirements listed above by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

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

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

across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

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

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

i. Description of the grouping and read-across approach proposed by you

You consider to achieve compliance with the REACH information requirements for:

- Sub-chronic toxicity study (90-day) (Annex IX, section 8.6.2.);
- Screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- in vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- in vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.)
- in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

for the registered substance Violet sodium polysulfide aluminosilicate with a SOD-type framework structure (Ultramarine violet), hereafter the 'target substance' or 'registered substance', using data of a structurally similar substance Blue sodium polysulfide aluminosilicate with a SOD-type framework structure (ultramarine blue) (EC number: not applicable, previously 309-928-3), hereafter the 'source substance'.

You have provided a "Read-across approach justification: Ultramarine blue and ultramarine violet" document as an Appendix in the CSR and "Reporting format for the analogue approach" document as a separate file, attached under the toxicity and ecotoxicity endpoints in the IUCLID dossier.

You have provided the following hypothesis: "*The analogue ultramarine blue shares the same functional group with the substance ultramarine violet. Therefore, they are expected to be toxicologically equivalent*". You also state that "*Ultramarine Pigments are treated as a group because their similar and close chemical structure: functional groups and chemical class, similar reactive profiles and behaviour, common precursors, and same physicochemical and toxicological characteristics that allow expecting a similar model/mechanism of action, similar toxicokinetic behaviour and bioavailability. All members are similar and follow a regular pattern*".

ECHA considers that this information is your read-across hypothesis.

In summary, you use the following arguments to support the prediction of properties of the target substance from data of the source substance:

- [redacted]Structure similarity: You state that the ultramarine pigments are UVCB substances, which are described as [redacted] You further state that [redacted]

- Physicochemical properties: you provided data showing that the physicochemical properties of the target and the source substances are in the "*same order*".

- Similar (eco)toxicological properties: you state that the same order of physicochemical properties "*...along with the similarity in the chemical structure and composition allow us to conclude that these "Ultramarine Pigments" will show the same or very similar toxicological and environmental behaviour*".

You conclude that "*the similarity in the chemical structure, composition and breakdown substances as well as the similarity in physicochemical properties and the available toxicological data, strongly suggest that the impact on the living organism and environment should not differ considerably*" between the source and target substance.

You further provide a data matrix for the source and target substances with a very brief summary of results of physiochemical, toxicological and ecotoxicological studies.

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

ECHA understands that your read-across hypothesis is based on structural similarity, on common precursors and breakdown products and on similarities in physico-chemical and (eco)toxicological properties. ECHA considers that there is insufficient information to support your read-across hypothesis, as explained in the following.

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

Structural (dis)similarities and their impact on the prediction

Structural similarity is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or in this specific case that structural similarity *per se* is sufficient to enable the prediction of human health and environmental properties of a substance, since structural similarity does not always lead to predictable or similar human health 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. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

In your read-across justification document you have established elements of structural similarities between the target and the source substances. You provide data on the quantitative composition and the different elements in the ultramarine pigments by X-Ray Fluorescence analysis. The data show that the main elements, which represent up to 97-98% of the material are: Si, Al, Na, S and O. Further, the crystal structure of Ultramarines was analysed by X-Ray Diffraction and confirmed by Infrared Spectroscopy (FTIR) and Nuclear Magnetic Resonance (NMR).

In your documentation you have also outlined structural differences between the target and the source substances. You state that the two substances differ in colour and that the different coloration is due to the different proportion of the polysulfides, $S_2^{\cdot-}$ and $S_3^{\cdot-}$ and S_4, which are encapsulated inside the β-cages. You indicate that the target substance shows major presence of S_4 chromophore (and less of $S_2^{\cdot-}$ and S_3), which is the most oxidised colour species. Further, you state that the main difference between the source and the target substance "is the Na content". Due to more oxidised status of the target substance "the Na content is smaller, and Si and Al contents slightly increase".

ECHA concludes that you have explained the obvious structural differences between the source and the target substance. However, you did not explain if those differences would lead to differences in their toxicity and ecotoxicity profiles.

Common precursors and breakdown products

In your read-across justification document you have provided information on the manufacturing process and the breakdown products. You state that the target substance is prepared from the source substance by [redacted] For the breakdown products you claim [redacted]. ECHA notes that you did not explain how this information would support your read-across hypothesis.

Similar physicochemical, toxicological and ecotoxicological properties

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 that you indicate that the impact of the source and the target substances on the living organisms "*should not differ considerably*" based on "[...] *similarity in physicochemical properties and the available toxicological data*".

ECHA acknowledges that the physicochemical properties of the target and source substances are within the same range.

However, ECHA considers that there is insufficient data supporting your claim of similarity in the (eco)toxicological properties of the source and the target substances, as explained below.

Firstly, ECHA notes that in the read-across justification you gave the following statement regarding the toxicity: "*Ultramarine Pigments are recognized as safe. No other pigment has had such long term and widespread human and environmental exposure without any reported instances of ill effect*". Further, you refer to the wide-spread use of the Ultramarines as a whitening additive in sugar and as a clothes whitening agents. You state that "*This represents a test of safety in human ingestion and skin contact on a grand scale*".

However, you did not explain how these statements would support your read-across hypothesis.

Secondly, regarding the toxicological properties, ECHA notes that you have not provided any experimental studies with the registered substance, in particular, repeated dose toxicity or reproductive toxicity studies.

Regarding the ecotoxicological properties, ECHA notes that neither short-term nor long-term aquatic ecotoxicity data is available for the registered substance.

Finally, you also did not provide any data to substantiate your expectation of "*similar model/mechanism of action, similar toxicokinetic behaviour and bioavailability*".

Therefore, the (eco)toxicity profiles of the source and the target substance cannot be compared and your prediction that "*all members are similar and follow a regular pattern*" cannot be validated.

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

In your comments to the draft decision you acknowledge that the information provided in your read-across justification did not follow the format of the Read-Across Assessment Framework (RAAF), since this document was not available at the time of your dossier submission. However, you claim that most of the information referred as key Assessment Elements (AEs) in the RAAF is already available in your technical dossier.

ECHA emphasises that the RAAF provides a systematic method for assessing whether a read-across approach fulfils the requirements of REACH Annex XI section 1.5.

You challenge ECHA's rejection of your read-across approach based on REACH Annex XI section 1.5 claiming that ECHA:

- "*failed in adequately assessing the read-across hypothesis by negating the quality of the submitted information, failed to apply its own guidance*" (RAAF) related to structural similarity, similarity in physical-chemical properties, "*same*" breakdown products.

- did not provide you an option to improve your read-across

- "*contradicts the REACH Regulation principle of just testing on animals as a last resort, fails in acting proportionally*" by requesting animal studies.

ECHA has assessed the issues raised by you in your comments and notes the following.

- Contradicting information on what is your hypothesis

Based on the read-across justification document you provided, ECHA understands that you base your predictions on the hypothesis that different compounds have similar (eco)toxicological properties as a result of structural similarity (i.e. RAAF Scenario 2). You claim that the substances will show the same type of effects for (eco)toxicological properties.

At the same time, in your comments to the draft decision you further state that your read-across hypothesis is based on (bio)transformation to common products (i.e. RAAF Scenario 1). You indicate that source and target substances *"are extremely similar regarding the structure but also have the same breakdown products"* and that *"information on common breakdown products are a basic element at this stage (..) and it is obvious and the scientific background of read-across approach that common breakdown products will lead to the same effects."*

Based on the information provided in your comments, it is not clear which in fact is your final hypothesis: structural similarity or common breakdown products. Regarding the claim of common breakdown products, you have not identified what are the common product(s) that would drive the impact on the property under consideration and how these common product(s) are formed, nor have you provided any supporting evidence. Hence, you have not justified the hypothesis of common breakdown products.

Regarding your hypothesis based on structural similarity, as already explained in the draft decision, ECHA agrees with the information provided on the structural (dis)similarities and similarity in physical-chemical properties. However, ECHA reiterates that similarity in structure and in physico-chemical properties alone is not sufficient to predict similar (eco)toxicological properties. Evidence is needed to prove that the data matrix supports the prediction, e.g. experimental data with the target and the source that enable comparison of the (eco)toxicological properties. This critical scientific aspect is described not only in the RAAF (e.g. AE A.4), but also in the ECHA Guidance Chapter R.6 (May 2008) (e.g. Section R.6.2.6.1).

You further indicate that you will update your dossier by providing more information demonstrating the nature and behaviour of source and target substances regarding breakdown products in different conditions, as well as supporting information on other chemicals with a similar composition that have been thoroughly tested. ECHA acknowledges your intention to gather additional information to support and refine the read-across approach. For other tests than those specified in Annexes IX and X to REACH you do not need to submit testing proposals, and it is in your discretion to conduct such studies without prior consent by ECHA.

ECHA further notes that you were informed in the notification letter to the draft decision that ECHA will not take any updates into account for the current decision making. ECHA notes that dossier updates and any new information therein will be evaluated by ECHA at the follow up stage.

- Possibility to improve your read-across

In several places in your comments to the draft decision you claim that ECHA did not give you *"any possibility for improvement and strengthening the read-cross hypothesis"*.

As explained above, ECHA has rejected your read-across predictions in particular due to the lack of any (eco)toxicological data with the target substance that would allow comparing their (eco)toxicity properties.

ECHA by this decision also requests a screening for reproduction/development toxicity study (OECD TG 422) with the target substance (such study exists for the source substance). ECHA has made a clear point that if similar target organ effects and NOAELs as found with the source substance are observed, this might strengthen the read-across justification for the human health related endpoints. For aquatic toxicity, your read-across justification can also

be strengthened if similarity in ecotoxicological data is demonstrated between target (for which no data is available and is requested) and source (for which data is available but their reliability cannot be currently assessed, as explained under points 5. and 6.).

As further explained to you already in the Notification letter accompanying the draft decision of 1 August 2018, updates of your registration dossier, and this includes information to support your adaptation, will be examined after the expiry of the deadline set in this decision in the follow-up evaluation under Article 42 REACH.

- Animal testing

In your comments to the draft decision, you claim that ECHA "*contradicts the REACH Regulation principle of just testing on animals as a last resort*" by requesting animal studies.

ECHA draws your attention to the fact that for each registered substance, standard information requirements have to be fulfilled, in your case those set out in Annexes VII-IX to REACH. You may use adaptations to the standard information requirements relying on provisions in Column 2 for specific information requirements in Annexes VII-IX or on general provisions in Annex XI.

REACH aims for a high level protection of human health and the environment. It represents the balance found in the legislative process between the need for information on hazardous properties of chemicals, which may involve animal testing, and the aim of avoiding unnecessary vertebrate animal tests.

Where REACH requires standard information for the registered tonnage band and you provide neither the information nor an adaptation according to the rules set out in REACH, then ECHA is held to request the missing information. Such a request cannot *per se* be disproportionate as you seem to argue.

In this sense, ECHA does not agree with your statement that current requests contradict the REACH Regulation principles on animal testing.

ii. Conclusion on the read-across approach

On the basis of the currently available information, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. In particular, you have demonstrated that the target and the source substances are structurally similar, however due to lack of explanation of the impact of structural differences on the predictions and in particular due to the lack of any (eco)toxicological data with the target substance, your hypothesis that the two substances would show similar (eco)toxicological properties cannot be proved. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

ECHA points out that if the OECD TG 422 study performed with the target substance (that ECHA requests by this decision) results in similar target organ effects and NOAELs as found with the source substance, this might strengthen the read-across justification for the human health related endpoints. For the environment related endpoints reliable long-term aquatic ecotoxicity data with both the target and the source substance would be needed to allow comparison of their ecotoxicological properties.

1. Water solubility (Annex VII, Section 7.7.)

"Water solubility" is a standard information requirement as laid down in Annex VII, Section 7.7 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 provided the results of a water solubility study according to OECD 105/EU A.6 test guideline using the column elution method. You report a water solubility value of 1.6 mg/L at 20 °C and pH 6.79 – 6.98. You report the selection of the method to be based on a preliminary water solubility test without providing any raw data from the preliminary test. In addition, you justify the selection of column elution method with water solubility being < 0.01 g/L in the preliminary test.

According to ECHA Guidance R.7a[2] a column elution method is suitable for essentially pure organic substances. The registered substance is an inorganic UVCB and therefore, the column elution method is not an appropriate choice to determine the water solubility for this type of substances. The results reported by you cannot therefore be considered reliable.

Regarding the sensitivity of test method, other test methods can be used to detect water solubility below 0.01 g/L (e.g. ECHA Guidance R.7a mentions that the flask method can measure water solubilities down to 1 µg/L).

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.

In your comments to the draft decision you indicated that you are willing to perform a new water solubility study according to the flask method, although the EU A.6 test guideline recommends the column elution method for substances with low solubility (<0.01 g/l). ECHA highlights that the flask method is more suitable for mixtures (as the registered substance is) and can also be applied to low solubility substances, provided that slow-stirring technique is used, as explained in the ECHA Guidance R.7a.

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: Water solubility (test method: OECD TG 105).

Guidance for determining appropriate test methods for the water solubility is available in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a, Section R.7.1.7.

2. 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 as laid down in Annex VII, Section 8.4.1. 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.

[2] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, Version 6.0, July 2017

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records for an *in vitro* gene mutation study in bacteria (OECD TG 471) with the analogue substance Ultramarine Blue (EC no 309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the 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.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

3. 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 in vitro micronucleus study" is a standard information requirement in Annex VIII, Section 8.4.2. to the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* mammalian chromosome aberration test (test method OECD TG 473) with the analogue substance Ultramarine blue (EC no. 309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the information requirement is rejected.

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

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

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

present decision: In vitro mammalian chromosome aberration test (test method: OECD TG 473) or in vitro mammalian cell micronucleus study (test method: OECD TG 487).

4. 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, Section 8.4.3. to the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain adequate study records for this endpoint. Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under 2. and 3. have negative results. 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 an *in vitro* gene mutation study in mammalian cells (OECD TG 476) with the analogue substance Ultramarine blue (EC:309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the information requirement is rejected.

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

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: In vitro mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490) provided that both studies requested under 2. and 3. have negative results.

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a screening for reproductive/developmental toxicity study (OECD TG 422) with the source substance Ultramarine blue (EC:309-928-3).

As explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the information requirement is rejected.

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

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

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

In your comments to the draft decision, you do not agree to conduct the requested study *"until the read-across hypothesis rejection will be fully justified by ECHA"*. ECHA has addressed your comments in section 'Grouping of substances and read-across approach' above and notes that the read-across adaptation is currently not supported.
Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

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

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

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

A "Sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a sub-chronic toxicity study (90-day) (OECD TG 408) and screening repeated dose/reproductive toxicity study (OECD TG

422) with the analogue substance Ultramarine blue (EC number: not applicable*, previously 309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" 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 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is reported to occur as a solid powder. 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, you do not agree to conduct the requested study "*until the read-across hypothesis rejection will be fully justified by ECHA*". ECHA has addressed your comments in section 'Grouping of substances and read-across approach' above and notes that the read-across adaptation is currently not supported.

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.

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

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

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the analogue substance Ultramarine blue ((EC number: not applicable, previously 309-928-3).. However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your read-across adaptation is rejected.
Furthermore, ECHA notes that the OECD TG 422 study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations.

Therefore, your adaptation of the information requirement is rejected.

In addition, you have also provided one non-guideline, non GLP compliant developmental study, performed with the registered substance, administered in the diet for only 7 days before mating ([redacted] *1966*). You have assigned a reliability score of 3 (not reliable), due to "*significant methodological deficiencies. The study is not well documented*". ECHA agrees that this study is not reliable, and it also does not cover key parameters of a pre-natal developmental toxicity study.

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

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

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

In your comments to the draft decision, you do not agree to conduct the requested study "*until the read-across hypothesis rejection will be fully justified by ECHA*". ECHA has addressed your comments in section 'Grouping of substances and read-across approach' above and notes that the read-across adaptation is currently not supported.

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

8. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing as the key study a study record for a "*OECD / Toxicity to aquatic algae and cyanobacteria / Toxicity to aquatic algae and cyanobacteria.002-MITI Japan / Violet sodium polysulfide aluminosilicate with a SOD-type framework structure / Violet sodium polysu...*" (according to "*NF T90-375 /NF EN 28692*") with the analogue substance(s) Blue sodium polysulfide aluminosilicate with a SOD-type framework structure (ultramarine blue) (EC number: not applicable, previously 309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the information requirement is rejected.

Furthermore, ECHA notes that the reporting of the read-across study submitted as the key study does not fulfill the requirements of Articles 10(a)(vii) of the REACH Regulation defining that the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I.

Article 3(28) of the REACH Regulation defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. ECHA notes that you have not provided sufficient information in the technical dossier to allow the assessment of the reliability of the read-across study submitted as the key study. In particular, as neither nominal nor measured test concentrations nor information on test solution preparation is reported, the actual exposure concentrations are unknown and it is not possible to assess whether the result of "*> 99mg/L*" is representative of the exposure. It is also not possible to assess whether the requirement of paragraph 39 of the OECD TG 201 of test concentrations being maintained within 20 % of the nominal throughout the test has been fulfilled. Furthermore, while ECHA acknowledges that you have indicated that validity criteria were fulfilled in the study, no information on biomass and on growth rates in the control cultures during the test is given. Thus, it is not possible for ECHA to verify whether the validity criteria as specified in the OECD TGD 201, paragraph 11, were met.

Therefore, your adaptation of the information requirement 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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

In your comments to the draft decision, you do not agree to conduct the requested study "*until the read-across hypothesis rejection will be fully justified by ECHA*". ECHA has addressed your comments in section 'Grouping of substances and read-across approach' above and notes that the read-across adaptation is currently not supported.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

9. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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 IX, Section 9.1.5., column 2. You provided the following justification for the adaptation "*In accordance*

with column 2 of REACH Annex IX, the long-term toxicity testing on invertebrates (required in section 9.1.5) does not need to be conducted as the chemical safety assessment indicates no need to investigate further the effects on aquatic organisms".

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 because of the following.

ECHA notes that neither short-term nor long-term aquatic ecotoxicity data is available for the registered substance. As explained above in Appendix 1, section "Grouping and Read-across Approach", your read-across adaptation submitted for the present endpoint and that of Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.) is not accepted. Therefore, ECHA considers that the available information in your chemical safety assessment cannot be used to adapt this standard information requirement.

ECHA considers also that long-term aquatic testing is required to accurately assess the potential ecotoxicity effects of your substance to aquatic organisms due to the following reasons. While the water solubility of your substance is questionable (please refer to request 1.), based on the information provided and due to substance properties the water solubility can be assumed to be low. Poorly soluble substances require longer time to be taken up by test organisms and therefore steady-state conditions are likely not reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance during an acute study.

ECHA hence considers that it is not possible to derive a reliable PNEC for a poorly water soluble substance with acute data alone, particularly when no effects are observed in acute studies. For the derivation of PNECaquatic reliable information on three trophic levels is required. Hence long-term data on aquatic plants (request 5.), invertebrates (request 6.) and fish (request 7.) are required to derive a reliable PNEC and to carry out a risk assessment.

Information on long-term toxicity testing on aquatic organisms shall also be considered for the classification and labelling of the substance. Hence if toxicity is observed in the studies to be conducted, the classification of the substance might have to revised.

In addition, 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 *"OECD / Long-term toxicity to aquatic invertebrates / Long-term toxicity to aquatic invertebrates.001-MITI Japan / Violet sodium polysulfide aluminosilicate with a SOD-type framework structure / Violet sodium polysu..."* (OECD TG 211) with the analogue substance Blue sodium polysulfide aluminosilicate with a SOD-type framework structure (ultramarine blue) (EC number: not applicable, 309-928-3).

However, as explained above in Appendix 1, section "Grouping and Read-across Approach" your adaptation of the information requirement is rejected.

Furthermore, ECHA notes that the reporting of the read-across study submitted as the key study does not fulfill the requirements of Articles 10(a)(vii) of the REACH Regulation defining that the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I.

Article 3(28) of the REACH Regulation defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. ECHA notes that you have not provided sufficient information in the technical dossier to allow the assessment of the reliability of the read-across study submitted as the key study. In particular, as neither nominal nor measured test concentrations nor information on test solution preparation is reported, the actual exposure concentrations are unknown and it is not possible to assess whether the results provided are representative of the exposure. It is also not possible to assess whether the requirement of paragraph 48 of the OECD TG 211 of test concentrations being maintained within 20 % of the nominal throughout the test has been fulfilled. Furthermore, while ECHA acknowledges that you have indicated that validity criteria were fulfilled in the study, no information on the test organisms and the control organisms is provided. Hence it is not possible to assess whether the validity criteria specified in the OECD TGD 211, paragraph 8, relating to mortality of parent organisms and mean number of live offspring produced per parent, were met.

Therefore, your adaptations of the information requirement 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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

In your comments to the draft decision, you do not agree to conduct the requested study "*until the read-across hypothesis rejection will be fully justified by ECHA*". ECHA has addressed your comments in section 'Grouping of substances and read-across approach' above and notes that the read-across adaptation is currently not supported.

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: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

10. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) 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 IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH Annex IX, the long-term toxicity testing on fish (required in section 9.1.6) does not need to be conducted as the chemical safety assessment indicates no need to investigate further the effects on aquatic organisms.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2., since - as fully discussed under point 6. above - there is no aquatic ecotoxicity data available for the registered substance and therefore the chemical safety assessment cannot be used to adapt this standard information requirement. As also fully explained under point 6. above, long-term data on aquatic plants (request 5.), invertebrates (request 6.) and fish (request 7.) are required to derive a reliable PNEC and to carry out a hazard and risk assessment.

Therefore, your adaptation of the information requirement 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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Section R.7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

In your comments to the draft decision, you do not agree to conduct the requested study "*until the read-across hypothesis rejection will be fully justified by ECHA*". ECHA notes that no read-across adaptation according to Annex XI Section 1.5 has been provided for this endpoint, since no source study is currently available in the technical dossier. ECHA points out that long-term toxicity testing on fish is a standard information requirement for substances registered at 1000 tonnes or more unless the specific rules for adaptation in Annex IX, Section 9.1., column 2 or the general rules for adaptation in Annex XI are met. As already explained above, the current adaptation of this information requirement according Annex IX, Section 9.1.6., column 2 is not acceptable.

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration for requests 8 to 10

Once results of the aquatic tests requested above are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

ECHA notes that there are no short-term studies available on aquatic invertebrates or on fish for the registered substance. Therefore the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted. As the registered substance is likely poorly water soluble, long-term studies are indicated.

Due to the properties of the substance (e.g. low solubility, colour) you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

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 19 March 2018.

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, including your request for an extension of the commenting period on the draft decision. ECHA did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-65 written procedure and ECHA took the decision according to Article 51(6) 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 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 your Member State.

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

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

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