EUROPEAN CHEMICALS AGENCY

Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482451-50-01/F
Substance name: Cobalt zinc aluminate blue spinel
EC number: 269-049-5
CAS number: 68186-87-8
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 2 May 2017

## DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-0000003730-80-05/F of 4 July 2014 ("the original decision") ECHA requested you to submit information by 9 May 2017 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

**Your registration still does not comply with the following information requirement:**

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

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.

The scope of this compliance check decision is limited to the standard information requirements of Annex IX, Section 8.6.2. to the REACH Regulation.

You have to submit the requested information in an updated registration dossier by ***1 April 2021*. You also have to update the chemical safety report, where** relevant. The timeline has been set to allow for sequential testing.

## 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 Wim De Coen, Head of Unit, Hazard Assessment

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

**Appendix 1: Reasons**

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

In decision CCH-D-0000003730-80-05/F ("the original decision") you were requested to submit information derived with the registered substance for Sub-chronic toxicity study (90-day) endpoint.

In the updated registration subject to follow-up evaluation, you have provided an adaptation according to the Annex IX, Section 8.6.2, Column 2.

Regarding the Annex IX, Section 8.6.2, Column 2 adaptation *"The subchronic toxicity study (90 days) 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', particularly if such a pattern is coupled with limited human exposure."* as further explained below, ECHA considers that several of the criteria are not met.

With regards to *"insoluble"*, ECHA notes that you provided results of dissolution studies in five artificial physiological media (phosphate-buffered saline (pH 7.2), Gamble's solution (pH 7.4), artificial lysosomal fluid (pH 4.5), artificial gastric fluid (pH 1.7) and artificial sweat solution (pH 6.5)). You reported that the dissolution of the registered substance was mostly below limit of detection of the analytical method. However for example for the artificial gastric fluid, the release of aluminium, cobalt and zinc were 121 µg/L, 11 µg/L and 29 µg/L at the highest loading of 0.1 g/L, corresponding to a solubility of 0.3 %, 0.02 % and 0.03 % respectively. ECHA considers that the substance is soluble to a limited extent.

With regards to *"not inhalable"*, ECHA notes that you reported a Mass median aerodynamic diameter (MMAD) of 49.04 µm as particle size distribution of the registered substance. Therefore, ECHA observes that the registered substance is inhalable (particles that enter the respiratory system via the nose or mouth, D <100 µm). ECHA notes also that although based on the concurrent particle size analysis via inhalation deposition modelling with MPPD (Multiple Path Particle Dosimetry) an important fraction of the deposition occurs in the extra thoracic region, it is also predicted by the model that a fraction of the airborne material is deposited in the pulmonary alveoli (0.7%) and tracheo-bronchial region (0.6%). Based on the information provided, ECHA is of the opinion that it cannot be concluded that the substance is *"not inhalable"*.

With regards to *"no evidence of absorption"*, ECHA notes that in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 97.4 % cobalt, 105% aluminium and 100% zinc via urine and faeces. Further, you reported measurable quantities of zinc (0.01%) and cobalt (<0.006%) in urine during the first day in the single dose mass balance study. You also reported that 24 hour urine and plasma sampling in the 28-day limit dose test showed negligible uptake of the registered substance. For example, you reported following concentrations of chromium in male rat plasma: for test group the concentration was 0.053 µg/L, whereas for the control group, the concentration was 0.003 µg/L. Based on the information you provided, ECHA is of the opinion that it cannot be concluded that there is *"no evidence of absorption"*.

Regarding the *"limited human exposure"*, ECHA notes as already indicated above that the newly reported particle size distribution data of the registered substance indicates that it contains both inhalable and respirable particles. Additionally, ECHA observes that in the

report on the occupational exposure assessment attached to IUCLID Section 13 [redacted] you describe spraying applications of the registered substance by downstream users. ECHA notes that spraying application are normally connected to a certain degree of exposure and while in table 17 of the document you describe the industrial spraying in enclosed settings, the professional spraying applications involve a worker directly working over the article which indicates inhalation exposure to the registered substance. ECHA is of the opinion that it cannot be concluded that there is *"limited human exposure"*.

ECHA notes that compared to the data available when issuing the original decision, the new information described above provides substantial new and relevant information that should be taken into account in selecting the route of a sub-chronic repeated dose toxicity study. Based on the new information you provided on the particle size distribution indicating that the registered substance is both inhalable and respirable, ECHA has reassessed the most appropriate route of administration for the study. The information provided in the technical dossier, the chemical safety report and occupational exposure assessment attached to the IUCLID section 13 [redacted] on properties of the registered substance and its uses indicate that human exposure to the registered substance by the inhalation route is likely. More specifically, the substance is reported to occur as a dust with a significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm). In particular, you reported dustiness 100.35 mg/g and Mass median aerodynamic diameter of airborne fraction: MMAD = 49.04 µm. ECHA considers that inhalation route is the most appropriate route of administration, having regard to the likely route of human exposure. Hence, the test shall be performed by the inhalation instead of oral route using the test method EU B.29./OECD TG 413.

In your comments to the draft decision you provided comments for each of the conditions of the above mentioned adaptation according to Annex IX, Section 8.6.2, Column 2.

As regards *"insoluble"*, you asked whether the term "insoluble" has to be taken literally (and whether the definition includes a threshold) or whether it should be replaced by the term "negligible" since each substance is soluble at a specific amount. ECHA underlines that the REACH Regulation does not provide a threshold for the definition of "insoluble". Nevertheless, ECHA notes that the term "insoluble" cannot be replaced by "negligible" at the discretion of the registrant. As already reported above, ECHA considers that the substance is soluble to a limited extent.

With respect to the criteria *"not inhalable"*, you indicated that based on the dustiness testing only 10% of the sample has the propensity to become airborne under physical agitation. Additionally, you indicated that the MPPD model prediction of the sample deposition on the different regions of the respiratory tract indicates that the majority of inhaled particles will be rapidly cleared to the gastrointestinal tract either by swallowing or by mucociliary escalation. ECHA underlines that, as reported in the ECHA Guidance R.8, R.7.1.14, dustiness is a relative term and is dependent on the method chosen, the condition and properties of the tested bulk material, and various environmental variables in which the tests are carried out. Thus, different methods may provide different results. While the dustiness indicates the propensity of a material to become airborne under workplace conditions, the numeric value of dustiness does not give information on the particle size distribution. The mass median aerodynamic diameter (MMAD) of the airborne fraction determined during the dustiness test (49.04 µm (GSD 7.72)) indicates that the airborne fraction of the tested material is inhalable. In relation to the MPPD inhalation deposition

modelling, ECHA underlines that the predicted total deposition in the human respiratory tract (43.8%) does not contradict the information that some of the particles of the registered substance are of inhalable size. Based on the information provided, ECHA is of the opinion that it cannot be concluded that the substance is *"not inhalable"*.

In relation to the criteria "*limited human exposure*", you indicated that the professional spraying applications are niche applications and conducted for R&D purposes. You stated that they are conducted on an infrequent and short-time basis in dedicated spray booths and the workers wear personal protective equipment. You stated that these activities are conducted for 15 minutes per shift once a month and the percentage of the pigment is maximum [redacted] ECHA underlines that in the report on the occupational exposure assessment attached to IUCLID Section 13 [redacted] the duration of exposure corresponds to 4h/shift and notes that a concentration of [redacted] of pigment in the spraying application cannot be considered low. Overall, although ECHA understands that these uses are marginal compared to industrial ones, ECHA notes that also short-term and infrequent activities give an opportunity to the worker to be exposed to the aerosol generated during spraying tasks. Additionally there are no exposure estimates or monitoring data available for such activities. Therefore, ECHA considers that it cannot be concluded that there is "*limited human exposure*".

Regarding "*no evidence of absorption*", similarly to your comments to the criteria "insoluble", your reasoning about the non-guideline single dose mass balance study, please see above. Based on the information you provided, ECHA is of the opinion that it cannot be concluded that there is "*no evidence of absorption*". In addition, when talking about the "*assessment of the most relevant route*", you mentioned that "*the deposited material of the "head" and "tracheo-bronchial" region would actually impact the nose, pharynx and bronchi and is subsequently most likely swallowed.*" Besides ECHA's arguments on the criteria "*not inhalable*" and "*insoluble*" and as explained above, the particles, which will deposit extrathoracicly and subsequently swallowed, will be absorbed to a certain extent.

With regards to *"low toxicity activity"*, you provided new information from the newly generated 28-day limit dose test in order to demonstrate that the values of the main findings are within the historical control ranges (*Table 2: Comparison of selected haematological and biochemical parameters of control and treated animals with the historical control range for that parameter*). That information, which is not provided in the IUCLID dossier, would allow to consider those observations as non-adverse. ECHA notes that this information seems to indicate "*no evidence of toxicity in a 28-day 'limit test'*". However, as stated above, several other conditions of the adaptation according to column 2 of Annex IX section 8.6.2 are not met.

ECHA further notes that further to comparisons with historical control values comparsions with internal controls of the 28-day limit test are relevant. Thus, ECHA considers that, the presence of several changes, compared with the internal controls, in haematological and clinical biochemistry parameters, as well as in spleen weight, seems to indicate that the substance is absorbed and enters into the systemic circulation to a certain extent to influence those parameters. This is relevant for the discussion on the absence of systematic absorption (see above).

Furthermore, in your comments, you claim that inhalation is not the most suitable route of administration because the existing information for cobalt zinc aluminate blue spinel shows

that the registered substance is not irritating. The purpose of performing a subchronic toxicity study via inhalation route is the evaluation of potential adverse local or/and systemic effects. Therefore, the scope of this study goes beyond the detection of local respiratory tract irritation. For instance, the deposition and retention in the lung of the test chemical can potentially cause inflammatory, fibrotic, and proliferative lesions, as well as alveolar/bronchiolar neoplasms. You also argue that the available acute inhalation toxicity study did not show any systemic or local adverse effects in the respiratory tract. An acute toxicity study covers, neither the exposure duration to the test chemical, i.e. 4 hours compared with a repeated daily inhalation exposure to a test chemical for 90 days, nor the number of parameters evaluated.

Finally, ECHA notes that in your comments to the draft decision you proposed also an adaptation based on a read across approach according to Annex XI section 1.5 of REACH Regulation. The provided read-across hypothesis is based on the bioavailability and toxicity of the three main compounds of the registered substance, cobalt(II), zinc(II) and aluminium(III). However, you only listed several studies which '*will be assessed further*'. Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". Within this documentation "it is important to provide supporting information to strengthen the rationale for the read-across" (ECHA Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals; section R.6.2.2.1 Read-across). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the target substance can be predicted from the data on the source substances.

In order to support your claim that the target and source substances have similar properties for the endpoints under consideration in the read-across approach, you refer to their bioavailability and irritant properties. Whilst this data set suggests that the substances may be similar in relation to these properties, these studies do not inform on the repeated daily exposure toxicity properties of the target and source substances. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration. Therefore, in the absence of such documentation, and only referring to your future assessment of the listed studies, ECHA cannot verify that the properties of cobalt zinc aluminate blue spinel can be predicted from the data on the source substances.

As detailed above, the request in the original decision was not met. 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: Sub-chronic inhalation toxicity: 90-day study (test method: EU B.29./OECD TG 413) in rats.

## 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 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 within 30 days of the notification.

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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 decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.

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

4. 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.