EUROPEAN CHEMICALS AGENCY

Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482461-49-01/F
Substance name: Zirconium praseodymium yellow zircon
EC number: 269-075-7
CAS number: 68187-15-5
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 1 December 2017

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

By decision CCH-D-2114289282-44-01/F of 12 December 2014 ("the original decision") ECHA requested you to submit information by 19 December 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.

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), oral route (Annex IX, 8.6.2.; test method: OECD 408) in rats

In decision CCH-D-2114289282-44-01/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 Pr was 574 µg/L at the highest loading of 0.1 g/L, corresponding to a solubility of 0.6 %. ECHA considers that the substance is soluble to a limited extent.

With regards to *"not inhalable"*, ECHA notes that you newly reported the following particle size distribution data of the registered substance: D10: 3.3 µm; D50: 9.6 µm; D90: 21.8 µm. Therefore, ECHA observes that the registered substance is inhalable (particles that enter the respiratory system via the nose or mouth, D <100 µm), and also respirable (the respirable fraction is the portion of inhalable particles that enter the deepest part of the lung, the non-ciliated alveoli (D <10 µm) with a 50% cut at 4 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 alveaoli (0.9%) and tracheo-bronchial region (0.8%). 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 102% Praseodymium and 74.3% of Zirconium. Further, you reported measurable quantities of Praseodymium excreted in urine during the first day in the single dose mass balance study (no data given for Zirconium). Based on the information you provided, ECHA is of the opinion that it cannot be concluded that there is *"no evidence of absorption"*.

With regards to *"no evidence of toxicity in a 28-day 'limit test"* ECHA notes that in the newly generated 28-day limit dose test the following findings were observed at 1000 mg/kg bw/day. You reported statistically significant differences in haematological parameters, namely increased platelet counts in females and increased absolute monocyte and basophilic granulocyte counts in males, statistically significantly decreased albumin levels in

females and increased glucose and decreased chloride levels in males. In male rats, you reported statistically significant increase in hindlimb grip strength. Furthermore you reported statistically significant organ weight changes in males (increased absolute left epididymis weight, increased absolute right testis weight, increased absolute left kidney weight, increased absolute right kidney weight, increased relative spleen weight, and increased absolute spleen weight) and females (decreased relative heart weight). You considered the findings not test item related. However ECHA is of the opinion that this does not support a conclusion of "*no evidence of toxicity in a 28-day 'limit test'*".

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 18 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 44.61 mg/g and Mass Median Aerodynamic Diamater of airborne fraction: MMAD = 22.79 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 claim that the solubility is "negligible". You refer to the dissolution of zirconium, praseodymium and silica in zirconium praseodymium yellow zircon being low after 2 hours in gastric fluid, being <LOD, 348 µg/L and 26.8 µg/L respectively. This corresponds with a relative bioaccessibility of 0%, 0.35% and 0.027% of absorbable metal ions following oral exposure. You claim that in order to assess whether these values are toxicologically relevant, it needs to be compared with hazard data of the zirconium, praseodymium and silica assessment entities. ECHA notes that these assessment entities refer to a proposed read across approach, which is addressed further below. However, as regards "*insoluble*", as already stated above, ECHA notes that after 24h in artificial gastric fluid, the release of Pr was 574 µg/L at the highest loading of 0.1 g/L, corresponding to a

solubility of 0.6 %. ECHA considers that the substance is soluble to a limited extent and therefor it cannot be concluded that the substance is *"insoluble"*.

As regards *"not inhalable"* you claim that while the total deposition in the human respiratory tract predicted with the MPPD model is approximately 50%, only a very small sub-fraction (0.9%) of the inhalable particles will deposit in the pulmonary region of the respiratory tract, whereas the remaining portion is predicted to deposit in the tracheobronchial and extrathoracic region. Thus, the overwhelming majority of inhaled particles would be rapidly cleared to the gastrointestinal tract either by swallowing (particles depositing extrathoracically) or by mucociliary escalation and subsequent swallowing (particles deposited tracheobronchially). Based on this you conclude that oral route represents the major route of human exposure. ECHA notes that as already stated above, you reported a dustiness of 44.61 mg/g and a MMAD of airborne fraction: MMAD = 22.79 µm, i.e. the substance has a significant proportion of particles of inhalable size. ECHA considers that it cannot be concluded that the registered substance is *"not inhalable"* secondly as further explained below ECHA considers that the above data supports that *"inhalation route is the most appropriate route of administration, having regard to the likely route of human exposure"*.

As regards *"limited human exposure"* you clarify that the professional spraying application is a short-time and infrequent activity and relates to research and development work. You also provide a worst-case calculation assuming this task to be conducted for 15 minutes per shift (although reasonably assumed to only be conducted at maximum once a month) in order to illustrate the overall exposure contribution of this task. You also state that the percentage of the pigment in the spray is maximum [redacted]. ECHA notes that while this spray application is of short duration, it nevertheless creates an opportunity for the worker to experience a high exposure to the aerosols that are created during that spraying task. Furthermore a concentration of [redacted] of pigment in the spraying application cannot be considered such a low concentration that there would be no significant exposure during that task. ECHA considers that it cannot be concluded that there is *"limited human exposure"*.

As regards *"no evidence of absorption"* you refer to the mass balance study and urinary concentration data and also clarify that Zirconium excretion via urine was also negligible and below 0.000015% and that the control group showed a mean value of about 1.46 µg Zr/L whereas the dose group showed only slightly higher mean values of ca. 2.38 µg Zr/L. You acknowledge the lack of these data in the IUCLID file, due to analytical problems at the time of submission. ECHA notes that as already stated above, in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 102% praseodymium and 74.3% of zirconium via urine and faeces and measurable quantities of praseodymium (0.03 µg Pr/L). According to your new data there was also measurable quantities of zirconium in urine and higher, although only slightly, than among controls. ECHA considers that it cannot be concluded that there is *"no evidence of absorption"*.

As regards *"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. That information, which is not provided in the IUCLID dossier, would seem to allow considering those individual 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, comparisons with internal controls of the 28-day

limit test are relevant. ECHA considers that, the presence of multiple changes, compared with the internal controls, in haematological and clinical biochemistry parameters, as well as in organ weights and grip strength, 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 determining if systematic absorption via relevant routes of exposure takes place, as discussed above.

Finally ECHA notes that in your comments to the draft decision your 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, praseodymium, zirconium oxide/hydroxide, and silica/silicates. However, you have 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 the 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 all toxicity properties following repeated daily exposure of the target and source substances. Accordingly, this information is 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 Zirconium praseodymium yellow zircon can be predicted from the data on the source substances.

As regards the most relevant route of administration you comment that oral, rather than inhalation route is the most relevant. You justify this with the deposition data predicted by the MPPD model as well as the arguments that the existing information shows that the registered substance is not irritating and no systemic or local effects were seen in the acute inhalation study. ECHA notes that the purpose of performing a subchronic toxicity study via inhalation route is the evaluation of potential adverse local and/or systemic effects. Therefore, the scope of this study goes beyond the detection of local respiratory tract irritation. Secondly, an acute toxicity study covers, neither the exposure duration, number of parameters nor number of animals per dose of a sub-chronic repeated dose toxicity study.

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.