ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482463-45-01/F
Substance name: High-temperature calcination products of diiron trioxide and amorphous silica resulting in a glassy silica matrix; previous substance name: Reaction mass of Fumes, silica and diiron trioxide
EC number: 701-304-2; previous EC number: 909-981-8
CAS number: -
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 13 May 2019

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

By decision CCH-D-0000003731-78-07/F of 4 July 2014 ("the original decision") ECHA requested you to submit information by 5 June 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.

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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

In decision CCH-D-0000003731-78-07/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 silica and iron were 12.1 µg/L and 62.6 µg/L at the highest loading of 0.1 g/L, corresponding to a solubility of 0.02 % and 0.07 % respectively. 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: 7.8 µm; D90: 17.0 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 alveoli (2.9%) and tracheo-bronchial region (1.2%). 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. 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 110.7% iron via urine and faeces. Further, you reported measurable quantities of iron (0.016%) in urine during the first day in the single dose mass balance study (no data given for silica). 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 *"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 clinical biochemistry parameters, namely decreased bilirubin and increased sodium levels in males. You also reported decreased body temperature in males. Furthermore, you reported statistically significant organ weight changes in males (increased relative brain weight, decreased absolute right epididymis weight, increased relative left testis weight, increased relative heart weight, decreased absolute spleen weight, decreased relative thymus weight and decreased absolute thymus weight). The histopathological analysis also showed inflammatory lesions in different organs. 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 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 117.26 mg/g and Mass median aerodynamic diameter of airborne fraction: MMAD = 12.68 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 text 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 12% 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 shows 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 (12.68 µm (GSD 3.57)) indicates that it is inhalable. As already stated above, the particle size distribution indicates that the registered substance is inhalable and also respirable. In relation to the MPPD inhalation deposition modelling, ECHA underlines that the predicted total deposition in the human respiratory tract (62.5%) does not contradict the information that some of the particles of the registered substance are of inhalable size.

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 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. Finally, ECHA notes that the Registrant provided the exposure levels for inhalable dust obtained at different workplaces in table 15 of the report on the occupational exposure assessment. ECHA notes that the 95th percentile for the monitoring data of inhalable exposure to the pigment during calcination ([redacted]) and milling/mixing ([redacted]) exceeds the OEL for general inhalable dust (10 mg/m^3) while the highest estimate is [redacted] during milling/mixing. The reported levels demonstrate that exposure via inhalation route occurs during different tasks at the workplace. ECHA also notes that the Registrant introduced a bioaccessibility factor for one constituent (e.g. SiO_2). ECHA underlines that the bioavailability is not relevant since the occupational exposure assessment is performed for external exposure and the DNELs and OELs are generally expressed as external values. If internal exposure is assessed then bioavailability is taken into account. In such situation biomonitoring data shall be provided together with a DNEL expressed as internal value ($DNEL_{biomarker}$) (ECHA Guidance R.8, R.8.1.2.7). Therefore, ECHA considers that it cannot be concluded that there is "limited human exposure".

Regarding "*no evidence of absorption*", similarly to the your comments to the criteria "insoluble", ECHA already addressed that in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 110.7% iron via urine and faeces and measurable quantities of iron (0.016%) in urine during the first day in the single dose mass balance study (no data given for silica). Based on the information you provided, ECHA was of the opinion that it cannot be concluded that there is "no evidence of absorption".
Besides ECHA's comments on the criteria "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. 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'*". On the other hand, the presence of several changes, compared with the internal controls, e.g. organ weight changes in males (increased relative brain weight, decreased absolute right epididymis weight, increased relative left testis weight, increased relative heart weight, decreased absolute spleen weight, decreased relative thymus weight and decreased absolute thymus weight), as well as histopathological observations, such as inflammatory lesions in different organs, would prove that the substance is absorbed and enters into the systemic circulation to a certain extent.

Furthermore, in your comments, you claim that inhalation is not the most suitable route of administration because the existing information for reaction mass of fumes, silica and diiron trioxide 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 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 two main compounds of the registered substance, iron(III) and silica/silicates. 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". 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, ECHA cannot verify that the properties of reaction mass of fumes, silica and diiron trioxide 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. However, following a dossier update (submission number: [redacted] submission date: 13 May 2019) where you have taken into account ECHA's communication on change of substance identification (communication number: SUB-C-2114470249-43-01/F), ECHA has changed the registered substance name from **Reaction mass of fumes, silica and diiron trioxide** (submission number [redacted] submission date 30 May 2017) to **High-temperature calcination products of diiron trioxide and amorphous silica resulting in a glassy silica matrix** (submission number [redacted]; submission date 13 May 2019).

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.