Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482418-40-01/F
Substance name: Chromium iron oxide
EC number: 235-790-8
CAS number: 12737-27-8
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 30 May 2017

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

By decision CCH-D-0000003729-63-06/F of 28 May 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 (Annex IX, Section 8.6.2) and ECHA requests you to submit the following information:

Sub-chronic toxicity study (90-day), inhalation route (Annex IX, 8.6.2.; test method EU B.29/OECD TG 413) in rats

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 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.

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision.

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 accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100-1000 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.

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

In decision CCH-D-0000003729-63-06/F ("the original decision") you were requested to submit information derived with the registered substance for Sub-chronic toxicity study (90-day) endpoint.

On 30 May 2017, you submitted an update of your registration dossier. 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. Based on the above-mentioned update of your registration dossier, ECHA concluded the following.

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.

As regards "**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 1.5) 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 except for the artificial gastric fluid, where Cr and Fe concentrations were below 18 µg/L even at the highest loading of 0.1 g/L, referring to a solubility of < 0.018 %. ECHA considers that the substance is soluble to a limited extent.

As regards "**not inhalable**", ECHA notes that you newly reported particle size distribution data of the registered substance as following: D10: 1.4 µm; D50: 2.9 µm; D90: 5.9 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 nonciliated alveoli (D <10 µm) with a 50% cut at 4 µm). Based on the information provided, ECHA is of the opinion that it cannot be concluded that the substance is *"not inhalable"*.

As regards of "**no evidence of absorption**", ECHA notes that in the non-guideline single dose mass balance study with the registered substance, you reported recoveries 85.8% of chromium and 92.4% of iron. Further, you reported measurable quantities of the registered substance in urine 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 urine: for test group the concentration was 169 µg/l, whereas for the control

group, the concentration was 47.2 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"*.

As regards "**no evidence of toxicity in a 28-day 'limit test'**", in the first assessment on the basis of the registration dossier, ECHA noted 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 a haematological parameters in females, namely decreased haemoglobin content and increased absolute basophilic granulocytes, statistically significantly increased cholesterol and increased potassium in males and decreased sodium in females. In male rats, you reported statistically significant increase in forelimb grip strength and statistically significant increased organ weights were reported in males: brain, kidneys and liver.

Regarding the "**limited human exposure**", ECHA observes that in the report on the occupational exposure assessment attached to the IUCLID section 13 [redacted] you described 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 the you described the industrial spraying in enclosed settings, the professional spraying applications involve the 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 31.04 mg/g which corresponds to dust proportion of 3.104%, and calculated p1: 20.0% MMAD1 = 4.35 µm and p2: 80.0% MMAD2 = 61.04 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.

On 11 May 2018, you provided comments on the draft of this decision which ECHA addresses in the following.

In Section 1 of your comments on the draft decision you referred to each of the conditions of the above mentioned adaptation according to Annex IX, Section 8.6.2, Column 2.

As regards "**insoluble**", you questioned whether "insoluble" means solubility equals zero or whether a treshold exists and the definition should be replaced by "negligible". ECHA observes that the REACH Regulation does not provide a threshold for such definition.

Nevertheless, ECHA notes that the term "insoluble" cannot be replaced by "negligible" at your discretion since they are not synonyms.

In your comment, you refer to the dissolution of chromium, which was mostly below the limit of detection of the applied analytical method, or, for artificial gastric fluid (pH 1.5) a low concentration of Cr (1.2 µg/L) after 24 hours was dissolved.

You did not refer to the dissolution of iron in your comments. However, similarly as for the chromium, you provided a table with the dissolution results for iron. For the artificial gastric fluid, the table shows dissolution of 7.5 µg/L after 2 hours, and 17.5 µg/L after 24 hours. Additionally, dissolution of the iron was also measurable in the artificial lysosomal fluid (pH 4.5) at 1.5 µg/L after 2 hours and 7.9 µg/L after 24 hours. Therefore, ECHA considers that the substance is soluble to a limited extent.

As regards your comments in relation to the condition **"not inhalable"**, ECHA concludes that the particle size distribution and mass median aerodynamic diameter (MMAD) determined with different methods (the laser diffraction method and the dustiness test connected with the cascade impactor) demonstrate that the registered substance is inhalable.

As regards **"no evidence of absorption"** you discussed results of the mass balance study and urinary concentrations measured in the 28-day limit dose study.

You explained that the recoveries from the mass balance were in the meantime recalculated. By the recalculation, the recoveries increased from 85,8% to 89,11% for chromium and from 92.4% to 94.1% for iron. You included in the Annex II of your comments a section [redacted] in which you provided tables with the recalculated values of the mean and individual animal measurements (5 males and 5 females).

ECHA observes that based on the tables provided in Annex II of your comments, the recovery of iron after 72 hours ranged from 48,2% to 155,3%, and the mean was 94,1% (females 80.4%, males 107.8%). The unaccounted mass fraction of iron ranged from -50.55% to +56.5%, and the mean was 5.9%. The recovery of chromium after 72 hours ranged from 43.5% to 150.5% with the mean of 89.11% (females 75%, males 103.2%). The unaccounted mass fraction of chromium ranged from -50.5% to +56.5%, and the mean was 10.89%. Calculations of the standard and relative deviations were not provided by you.

You further stated that based on the mass balance experiment in which 10% of chromium could not be detected when calculating the mass balance, chromium has a very low absorbance ability within gastrointestinal tract (~0.1-2%). You further supported the conclusion by a parallel toxicokinetic study which demonstrated that chromium(III) has a relative bioavailability of < 0.077%. You also explained that the actually received dose did not fully correspond to the nominal dose, and stated that those aspects were not further addressed within the context of the study.

ECHA observes that you:

- did not include explanation how the recoveries were calculated originally and how were they recalculated, i.e., how and why the recovery could increase.
- did not explain in the comments the high variability of the recoveries in the individual animals and recoveries significantly exceeding 100%.

- did not address the discrepancies between nominal and actually received dose in the mass balance study

You questioned whether no systemic absorbption means absolute zero, and suggested that "no" should be replaced by "negligible". ECHA observes that the REACH Regulation does not provide a threshold for such definition. Nevertheless, ECHA notes that the "no" cannot be replaced by "negligible" at your discretion since they are not synonyms.

You further discussed results of the measurements of the urinary concentrations in the 28-day limit dose study. You explained that the mean concentration of chromium in urine of the animals was recalculated after an exclusion of an outlier. You concluded that *"a mean value of 5.66 ± 5.58 µg/L is calculated for chromium in male rat urine for the limit dose group 1,000 mg pigment /kg bw which is far below the control group (47.2 ± 53.2 µg Cr/L urine)."*

ECHA observes that the mean chromium concentration in the urine of control group, which was not exposed to the registered substance, is far above the mean chromium concentration of the limit dose group which received 1000 mg/kg bw/d of the registered substance. Also, the standard deviations of the mean concentrations are very high. Moreover, the standard deviation of the mean chromium concentration in the urine of the control group is higher than the mean concentration itself.

You have explained neither the high chromium concentration in urine of animals which were not dosed with chromium containing registered substance, nor the standard deviation exceeding the mean value itself. Based on the above described issues in the measurements of the urinary concentrations of chromium, ECHA cannot consider the measurements of the chromium in the urine of the animals from the 28-day study plausible.

For the reasons described above, the absence of systemic absorption via relevant routes of exposure cannot be confirmed. Based on the information provided, it cannot be concluded the condition of "*no evidence of absorption*" of the Annex IX, Section 8.6.2, Column 2 is met.

ECHA also observes that a study report amendment for the GLP mass balance study with the recalculated recoveries as provided in your comments is not included in the registration dossier. Nevertheless, ECHA notes that under GLP principles, *"it would not be appropriate to use a study report amendment to facilitate the reanalysis of data or add new data to a final report except under exceptional circumstances"*[2].

As regards of **"no evidence of toxicity in a 28-day 'limit test'"** you argued that based on the historical control ranges, the results can be interpreted as not adverse or to be due to a normal biological variation. You further considered the statistical significance of some of the findings to be a chance finding. You concluded that the statistically significant shifted parameters are within the normal variation and should be regarded as biologically irrelevant.

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*

[2] http://www.oecd.org/chemicalsafety/testing/glp-frequently-asked-questions.htm, Study reporting, point 1 "Under what circumstances can a GLP study be reopened after the final report has been finalised?"

evidence of toxicity in a 28-day 'limit test'". However, as stated above, several other condistions of column 2 of section 8.6.2 of Annex IX are not met.

ECHA further notes multiple statistically significant findings in haematology, biochemistry, functional observation battery parameters, and organ weights, when compared with the concurrent controls, seems to indicate that the substance is absorbed and enters into the systemic circulation to a certain extent to influence those parameters, contradicting the condition for the "absence of systemic absoprtion via relevant route of exposure". This is relevant for the discussion on '*no evidence of absorption*'(see above).

As regards your comments in relation to the condition "**limited human exposure**", and ECHA acknowledes that professional spraying is a short-time and infrequent activity. However, it gives an opportunity for the worker to be exposed to the aerosols that are created in the spraying task, also the concentration of [redacted] registered substance in sprayed formulation is rather high. In addition, there are other handling tasks than spraying where the formation of aerosol/dust is likely in the dossier. Examples of such tasks are mixing, transferring substance in undedicated facilities, roller and brushing application, high energy work-up of substance bound in/on materials and/or articles, handling of solid materials and maintenance of machinery (PROC 5, 8a, 10, 24, 26 and 28). In your monitoring data you estimated that the 90 percentile concentration for inhalable dust is [redacted] in calcination, and [redacted] in milling and mixing. The maximum concentration is [redacted] for inhalable dust which is [redacted] of the OEL for general inhalable dust (10 mg/m^3) and demonstrate that the exposure via inhalation is likely during the use of the registered substance.

ECHA maintains the view that the conditions for an adaptation according to Annex IX, Section 8.6.2, Column 2 are not fulfilled.

You further referred to the most relevant and appropriate route of administration in sections 1 and 2 of your comments. You commented 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. The available acute toxicity study covers does not cover the exposure duration, number of parameters or number of animals per dose of a sub-chronic repeated dose toxicity study
ECHA has reassessed the most appropriate route of administration for the study. Based on the new information you provided, in particular, the new information on the particle size distribution indicating that the registered substance is both inhalable and respirable, ECHA considers that the inhalation route is the most appropriate route of administration. Given that the Agency has changed the route of administration compared to the initial decision, the Agency has set a specific deadline for the data to be provided.

In section 2 and 3 of your comments, you suggested a read-across approach and listed findings of several supporting studies but did not provide robust study summaries for these that would enable ECHA to independently assess the studies.
You stated the following: *"We anticipate that based on the rationale provided above, read-across to soluble chromium and soluble iron substances will sufficiently address these*

information requirements. Thus, for the assessment of the toxicity of chromium iron oxide, data for chromium and iron are read-across since only the ions of chromium and iron, so called assessment entities, are available under physiological conditions and determine the toxicological potential of chromium iron oxide. A non-exhaustive overview of the references to be added as robust study summaries for the assessment entities chromium and iron is provided in Annex III".

ECHA assumes that you suggest to apply adaptation according to Annex IX, Section 1.5 to read-across from soluble chromium and iron to predict toxicological properties of the registered substance. Nevertheless, 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.

Therefore, in the absence of such documentation, ECHA cannot verify that the properties of the registered substance can be read-across from the soluble chromium and iron.

In summary, ECHA observes that the information provided does not fulfil the adaptation requirements of the Annex IX, section 8.6.2, Column 2 or Annex XI, Section 1.5.

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

This compliance check decision under Article 41 REACH, in conjunction with Article 42(1) of REACH, is necessary because in your updated registration you have provided new and relevant experimental information, which was not available to you or ECHA at the time when your registration was examined for the original decision.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the notification of this draft decision 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.

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.