ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482416-44-01/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:

Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route

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 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

Pre-natal developmental toxicity study in rats or rabbits, oral route

In decision CCH-D-0000003729-63-06/F ("the original decision") you were requested to submit information derived with the registered substance for Pre-natal developmental toxicity endpoint.

In the updated registration subject to follow-up evaluation, you have provided an adaptation according to the Annex IX, Section 8.7, Column 2, third indent and according to the Annex XI, Section 1.2 of the REACH Regulation. Based on above mentioned update of your registration, ECHA concluded the following.

Annex IX, Section 8.7, Column 2, third indent of the REACH Regulation states *"The studies do not need to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure."*
As further explained below, ECHA considers that none of the criteria are met.

As regards **"low toxicological activity"**, in the first assessment and the available information in the IUCLID 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 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: brain, kidneys and liver.

As regards **"absence of systemic absorption via relevant routes of exposure"**, ECHA notes that in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 85.8% for chromium and 92.4% for 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. ECHA is of the opinion that the data demonstrate absorption via oral route which is, based on the particle size distribution, a relevant route of exposure together with inhalation route due to ingestion of larger particles cleared from the respiratory tract. Based on the information provided, ECHA is of the opinion that it cannot be concluded that there is *"no systemic absorption via relevant routes of exposure"*.

As regards **"no or no significant human exposure"** 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 non-ciliated alveoli (D <10 µm) with a 50% cut at 4 µm). 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 you described 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 *"no or no significant human exposure"*.

With respect to the adaptation according to the Annex XI, Section 1.2, ECHA observes that the sources of information do not allow to conclude whether or not the registered substance has a particular dangerous property (i.e. developmental toxicity). In particular, none of the sources of information provides evidence about the potential of the registered substance to cause pre-natal developmental toxic effects, as the only repeated dose toxicity study does not examine pre-natal developmental endpoints. Also, as already pointed above, in ECHA's view, it cannot be concluded that the registered substance would show such general absence of toxicological activity and absorption, which would allow to conclude an absence of developmental toxicity as well.

On 18 April 2018, you provided comments on the draft decision which ECHA addresses in the following.

In Section 1 of your comments to the draft decision you provided comments for each of the conditions of the above mentioned adaptation according to Annex IX, Section 8.7, Column 2.

With regard to **"low toxicological activity"** you argued that based on the historical control ranges, information provided in your comments to the draft decision, the results can be interpreted as not adverse or to be due to a normal biological variation. You further argued the statistical significance of some of the findings to be a chance finding or 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 *"low toxicological activity"*. However, several other conditions of the adaptation are not met.

ECHA further notes multiple statistically significant findings in haematology, biochemistry, functional observation battery parameters, and organ weights which, when compared with the concurrent controls, seems to indicate that the substance is absorbed and enters into the systemic circulation to a certain extent, contradicting the condition *"absence of systemic absorption via relevant route of exposure"*. This is relevant for the discussion on the absence of systematic exposure, as discussed above.

With regard to your comments on **"absence of systemic absorption via relevant routes of exposure"**, you explained that the recoveries from the mass balance study were recalculated and increased from 85.8% to 89.11% for chromium and from 92.4% to 94.1% for iron. You included in 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 the recovery of iron after 72 hours ranged from 48.2% to 155.3%, and the mean was 94.1%. 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 mean 89.11%. The unaccounted mass fraction of chromium ranged from -50.5% to +56.5%, and the mean was 10.89%. Standard deviation calculation for the values was not provided by you.

You further stated that based on the experiment with chromium (III), although 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 the 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 results significantly exceeding 100%.
- did not address the discrepancies between nominal and actually received dose in the mass balance study

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 that the condition of *"no systemic absorption occurs via relevant routes of exposure"* of the Annex IX, Section 8.7, 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].

In relation to your comments to the criteria "**no or no significant human exposure**", ECHA observes the following:

- ECHA agrees with your argumentation concerning the particle size information obtained by the laser diffraction method and the dustiness test connected with the cascade impactor. However, it does not change the interpretation whether the registered substance is inhalable or not inhalable. Also the Mass median aerodynamic diameter (MMAD) calculated by the cascade impactor from the airborne fraction of the dustiness test is demonstrating that the airborne fraction is inhalable (MMAD1 = 4.35 µm (GSD = 1.1), MMAD2 = 61.04 µm (GSD = 9.09)). In conclusion, the particle size distribution and MMAD determined with different methods, as explained above, demonstrate that the registered substance is inhalable.
- In the comments you corrected that professional spraying task is conducted only 15 minutes per shift and once a month compared to 4 hours per shift in the Report on Occupational Exposure Assessment [redacted]

[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?"

[redacted] attached to the registration dossier. ECHA understands that it is short-time and infrequent activity but it anyway gives an opportunity for the worker to be highly exposed to the aerosols that are created in the spraying task.

- The concentration of the registered substance in the spraying application is [redacted] which cannot be considered as low concentration.
- There are also other handling tasks than spraying tasks 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 inorganic substances and manual maintenance of machinery (PROC 5, 8a, 10, 24, 26 and 28).
- In the monitoring data in the Report on Occupational Exposure Assessment [redacted] it was predicted 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. The measured concentrations are below the OEL for general inhalable dust (10 mg/m3), however, they demonstrate that exposure via inhalation is likely.

Based on the information provided, it cannot be concluded that the condition of "*no or no significant human exposure*" of the Annex IX, Section 8.7, Column 2 is met.

ECHA maintains the view that the conditions to adapt according to Annex IX, Section 8.7, Column 2 of the REACH Regulation are not fulfilled.

Further, in Section 2 of your comments "*Read-across approach for Chromium iron oxide and way forward*", you listed findings of several supporting studies. In Section 3 of your comments, you stated 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.*"

Based on the statements in Section 2 and 3 of your comments, ECHA assumes that you suggest to apply an adaptation according to Annex IX, Section 1.5 to read-across from soluble chromium and iron to predict toxicological properties of the registered substance.

ECHA also observes that you listed findings of several supporting studies and provided a list of references, but did not provide robust study summaries for these that would enable ECHA to independently assess the studies.

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. Furthermore, ECHA notes that among the studies listed there appear to be no studies on pre-natal developmental toxicity for the soluble chromium and iron, which could be used as source studies for the read-across.

In summary, ECHA observes that the information provided does not fulfil the adaptation requirements of the Annex IX, 8.7. Column 2 or Annex XI, Section 1.2 or Section 1.5.

As detailed above, the request in the original decision was not met, and you are still required to provide the pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

Appendix 2: Procedural history

This decision is necessary after the follow-up evaluation according to Article 42(1) of the REACH Regulation, because in your updated registration you have provided new 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 date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(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.