ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000002181-86-02/F Helsinki, 1 March 2012

DECISION on a compliance check of a registration pursuant to Article 41(3) of regulation (EC) no 1907/2006

For 00000 RP002- Fe(III)HBED, CAS 1061328-86-6 (EC Nr. 700-327-5), Registration Number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for 00000 RP002-Fe(III)HBED, CAS 1061328-86-6 (EC Nr. 700-327-5) submitted by [redacted] (Registrant), latest submission number [redacted], for 100 - 1000 tonnes per year.

The compliance check was initiated on 9 June 2010.

On 2 May 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 16 and 17 June 2011 the Registrant provided to ECHA comment on the draft decision, and on 20 July and 11 August 2011 the Registrant updated the dossier.

ECHA has taken into account the information received and amended the draft decision.

On 4 November 2011 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. ECHA reviewed the proposals for amendment received and decided to amend the draft decision.

On 8 December 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.
On 19 December 2011, the draft decision was referred to the Member State Committee.

On 28 December 2011 and 9 January 2012 the Registrant provided comments on the proposals for amendment and new information addressing issues not covered by the proposals for amendment. Pursuant to Article 51(5) of REACH Regulation the Member State Committee only took the Registrant's comments on the proposals for amendment into

account.

After discussion in the Member State Committee meeting on 6-10 February 2012, the Member State Committee further modified the draft decision and a unanimous agreement of the Member State Committee on the draft decision was reached on 9 February 2012.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

1) Pursuant to Articles 41(1)(a) and Annexes VII – IX of the REACH Regulation the Registrant shall submit the information using (where appropriate) the test method as indicated on

   a. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2, EU Method B.10 or OECD 487)
   b. Screening for reproductive/developmental toxicity, one species, rat (Annex VIII, 8.7.1, OECD guideline 421 or 422)
   c. Sub-chronic toxicity study (90-day) one species, rat (Annex IX, 8.6.2, EU Method B.26)
   d. Pre-natal developmental toxicity study, one species, rat, Annex IX, 8.7.2, EU Method B.31)
   e. Activated sludge respiration inhibition testing (Annex VIII, 9.1.4, EU Method C.11)
   f. Effects on terrestrial organisms (Annex IX, 9.4; Test on toxicity to terrestrial plants: OECD guideline 208 or ISO standard 22030)
   g. Toxicokinetics assessment (Annex VIII, 8.8.1)

2) Pursuant to Articles 41(1)(c), 14 and Annex I of the REACH Regulation the Registrant shall submit in the Chemical Safety Report:

   a. Identification of DNEL(s), (Annex I, 1.4.)
   b. Identification of the PNEC, (Annex I, 3.3.1.)
   c. PBT assessment, (Annex I, section 4)
   d. The estimated exposure (Exposure_scenario and exposure estimation) and the risk characterisation for human health and environment (Annex I, sections 5 and 6). The exposure assessment and the risk characterisation shall cover all stages of the life-cycle of the substance, including preparations.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcomes and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation. The Registrant shall consult the Guidance on information requirements and chemical safety assessment (Version 1.1., May 2008, Chapter R.7.A, Section R.7.6.6.3., page 365) to follow the integrated testing strategy for reproductive toxicity testing. In general, it should be noted that the OECD TG 414 (EU B.31) study does not incorporate post-natal parameters and therefore it is advisable not to bypass the screening study when a prenatal developmental toxicity study is triggered.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by 1 March 2014.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance in accordance with Article 6 of the REACH Regulation, does not comply with the requirements of Articles 10, 12 and 13 and with Annexes I, VII, VIII, IX and XI thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

1) Missing information related to endpoints

Pursuant to Articles 10(a)(vi), 12(1)(a) and (b) of the REACH Regulation, a registration for a substance produced in quantities of 100 – 1000 tonnes per year shall contain as a minimum the information specified in Annex IX of the REACH Regulation.

1.1. The technical dossier contained adaptations to the standard information requirements for the endpoints on:

a. *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2, EU Method B.10 or OECD 487)
b. Screening for reproductive/developmental toxicity, one species, rat (Annex VIII, 8.7.1, OECD guideline 421 or 422)
c. Sub-chronic toxicity study (90-day) one species, rat (Annex IX, 8.6.2, EU Method B.26)
d. Pre-natal developmental toxicity study, one species, rat, Annex IX, 8.7.2, EU Method B.31)
e. Activated sludge respiration inhibition testing (Annex VIII, 9.1.4, EU Method C.11)
f. Effects on terrestrial organisms (Annex IX, 9.4; Test on toxicity to terrestrial plants: OECD guideline 208 or ISO standard 22030

a. Mutagenicity, *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VII, 8.4.2)

The Registrant has adapted the standard data requirements for these endpoints based on general findings and properties of a chelating agent HBED. No information on the structure and possible similarity of HBED to the registered substance has been submitted. In addition, the Registrant refers to (i) toxicological and ecotoxicological studies conducted with the registered substance, (ii) a mutagenicity study that has been "positively tested", (iii) use of the substance only in agriculture in very small concentrations, (iv) limited exposure time to living organisms, and (v) 3R –principle.

According to Annex VIII, Column 2, 8.4.2, the study does not usually need to be conducted if adequate data from an *in vivo* cytogenicity test are available, or the substance is known to be carcinogenic category 1 or 2 or mutagenic category 1, 2 or 3. According to Annex VIII, Column 2, 8.4.3, the study does not usually need to be conducted if adequate data from a reliable *in vivo* mammalian gene mutation test are available. In addition, Annex XI, section

1.5, sets out the general rules for adaptation of the standard testing regime when grouping of substances and read-across approach is used.

The waiving justifications provided by the Registrant do not meet any of the criteria set out in Annex VIII, Column 2, 8.4.2 and 8.4.3. In addition, the conditions for grouping of substances and read-across approach as set out in Annex XI, section 1.5. are not met.

In response to ECHA's draft decision, the Registrant submitted data on structural similarities between the registered substance and the read-across substance, [redacted] three studies conducted with that read-across substance, a statement of [redacted] and *in vitro* mammalian chromosome aberration and *in vitro* mammalian cell gene mutation test conducted with another read-across substance, [redacted]. ECHA notes that the registered substance and the read-across substance [redacted] are structurally similar. However, the studies conducted with [redacted] are not genotoxicity studies, and the general statement on the physical-chemical properties of [redacted] does not support the read-across justification. The Registrant has not provided any justification for the use of genotoxicity studies conducted with [redacted]. Therefore, ECHA concludes that the additional information provided by the Registrant does not meet the criteria set out in Annex VIII, Column 2, 8.4.2 and 8.4.3, and Annex XI, section 1.5.

Therefore, the Registrant is requested to submit an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, 8.4.2, EU Method B.10 or OECD 487).

Furthermore, the registrant is reminded that, according to the result of the requested test, additional genotoxicity studies may be required according to Annex VIII, 8.4.3 and Column 2, 8.4. Further guidance on genotoxicity testing can be found in the Guidance on Information Requirements and Chemical Safety Assessment, R.7.7.6.3, Testing strategy for mutagenicity.

b. <u>Screening for reproductive/developmental toxicity, one species, rat (Annex VIII, 8.7.1, OECD guideline 421 or 422)</u>

The Registrant has adapted the standard data requirement for this endpoint based on no systemic absorption via relevant routes of exposure and no significant human exposure.

The justification for waiving provided by the Registrant does not meet the conditions of Annex VIII, Column 2, 8.7.1 since the pre-natal developmental toxicity study is not available, nor does it constitute a waiving according to REACH, Annex XI.

c. <u>Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2)</u>

The Registrant has adapted the standard data requirement for this endpoint based on (i) the use of the substance only in agriculture in very small concentrations, (ii) limited exposure time to workers, (iii) lack of acute toxicity, (iv) 3R –principle, and (v) Annex XI, 3.1, exposure scenario, and on safety report where no repeated exposure was found.

First, according to Annex IX, Column 2, 8.6.2, a sub-chronic toxicity study (90 days) does not need to be conducted if (i) a reliable short-term toxicity study (28-day) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty

factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure, or (ii) a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used, or (iii) the substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake), or (iv) 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.

These justifications for waiving provided by the Registrant do not meet the conditions of Annex IX, Column 2, 8.6.2.

Second, Annex XI, 3.1. of the REACH Regulation allows the registrant to waive a study based on the exposure scenarios developed in the Chemical Safety Report.

Indeed, section 9, Exposure assessment, of the Chemical Safety Report the Registrant states that "does not result in exposure". However, the Registrant did not provide an exposure scenario.

Therefore, the conditions for waiving the study under Annex XI, section 3.1., have not been met.

In response to ECHA's draft decision, the Registrant submitted data on structural similarities between the registered substance and the read-across substance, [redacted], two studies conducted with that substance, and oral and dermal repeated dose (90-day) toxicity studies conducted with another read-across substance, [redacted]. ECHA notes that the registered substance and the read-across substance [redacted] are structurally similar but the studies conducted with [redacted] are not sub-chronic or chronic studies. The Registrant has not provided any justification for the use of oral and dermal repeated dose (90-day) toxicity studies conducted with [redacted].
No new information on the exposure was provided. Therefore, ECHA concludes that the additional information provided by the Registrant does not meet the criteria set out in Annex IX, Column 2, 8.6.2, Annex XI, sections 1.5. and 3.1.

The Registrant is reminded that on the basis of the results of the 90-day study, it should consider whether a two-generation reproductive toxicity study is required (Annex IX, 8.7.3) and submit a testing proposal for such study if necessary.

d. Pre-natal developmental toxicity study (Annex IX, 8.7.2)

The Registrant has waived the test based on the other studies that show the safety of the substance. The Registrant refers to negative result of the Ames test.

According to Annex IX, Column 2, 8.7.2, the study does not need to be conducted if (i) the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or (ii) the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or (iii) 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 the metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

In response to ECHA's draft decision, the Registrant submitted data on structural similarities

between the registered substance and the read-across substance, [redacted], five studies conducted with that substance, and one-generation reproductive toxicity and pre-natal developmental toxicity studies conducted with another read-across substance, [redacted] In addition, the Registrant refers to Annex IX column 2, 8.7. and states that the studies need not to be conducted since no systemic absorption occurs via relevant routes of exposure and no significant human exposure exists. ECHA notes that the registered substance and the read-across substance [redacted] are structurally similar but the studies conducted with [redacted] do not address developmental toxicity, no toxicokinetic data has been submitted to prove the lack of absorption of the registered substance, and no exposure scenario has been submitted. In addition, the Registrant has not provided any justification for the use of one-generation reproductive toxicity and pre-natal developmental toxicity studies conducted with [redacted]. Therefore, ECHA concludes that the additional information provided by the Registrant does not meet the criteria set out in Annex IX, Column 2, 8.7.2., and Annex XI, section 1.5.

The justification for waiving provided by the Registrant does not meet any of the conditions of Annex IX, Column 2, 8.7.2.

e. Activated sludge respiration inhibition testing (Annex VIII, 9.1.4)

The Registrant has waived testing on activated sludge respiration inhibition based on the safety of the substance by referring to results of the following tests: *Pseudokirchneriella subcapitata* growth inhibition test, *Daphnia magna* reproduction test, Fish sub acute toxicity test for *Oncorhynchus mykiss Walb.*, metabolism of nitrogen, metabolism of carbon and Ames test.

According to Annex VIII, Column 2, 9.1.4, activated sludge respiration inhibition testing does not need to be conducted if (i) there is no emission to a sewage treatment plant, (ii) there are mitigating factors indicating that microbial toxicity is unlikely to occur, for instance the substance is highly insoluble in water, or (iii) the substance is found to be readily biodegradable and the applied test concentrations are in the range of concentrations that can be expected in the influent of a sewage treatment plant.

The justification for waiving provided by the Registrant does not meet the conditions of Annex VIII, Column 2, 9.1.4, nor does it constitute a waiving according to REACH, Annex XI.

f. Effects on terrestrial organisms (Annex IX, 9.4; Test on toxicity to terrestrial plants: OECD guideline 208 or ISO standard 22030

According to REACH Annex IX, 9.4.3, testing on short-term toxicity to plants is an information requirement. According to Annex IX, 9.4, column 2, the study does not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. In the absence of toxicity data for soil organisms, the equilibrium partitioning method (EPM) may be applied to assess the hazard to soil organisms. The choice of the appropriate tests depends on the outcome of the chemical safety assessment. Annex IX, 9.4 requires the Registrant to perform short-term studies, but column 2 mentions "*In particular for substances that have a high potential to adsorb to soil or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term*".

The Registrant has waived testing on short-term toxicity to plants based on the safety of the substance by referring to results of the following tests: '*Pseudokirchneriella subcapitata*

growth inhibition test, *Daphnia magna* reproduction test, Fish sub acute toxicity test for *Oncorhynchus mykiss Walb.*, metabolism of nitrogen, metabolism of carbon and Ames test.'

The justification for waiving provided by the Registrant does not meet the conditions of Annex IX, Column 2, 9.4.3 nor does it constitute a waiving according to REACH, Annex XI.

In the updated dossier the Registrant has provided a study summary of a study examining [redacted] effects of the registered substance. The Registrant reports that [redacted] were observed up to a concentration of [redacted]/kg soil. This corresponds to a concentration of [redacted]/kg soil. This is [redacted] than what is usually tested in terrestrial studies [redacted]

Therefore, the dossier does not contain data to fulfil the information requirement of REACH Annex IX, 9.4.3, short-term toxicity to plants.

Based on the information in the dossier the Registrant may consider long-term toxicity testing more appropriate to fulfil the information requirements. According to Guidance R.7c, Table R.7.11-2, the registered substance falls into 'hazard category 3'. Therefore, the guidance advises registrants to perform the hazard assessment using the EPM (with a PEC x 10) AND conduct a confirmatory long-term soil toxicity test as a first step. The results of the EPM approach and the long term toxicity test may indicate the need of further confirmatory long term toxicity testing.

Therefore, the Registrant shall perform a study according to ISO standard 22030 or OECD guideline 208.

The justifications provided by the Registrant for adapting the studies listed above do not fulfil the criteria set out in Annexes VII – IX, Column 2, nor Annex XI. Therefore, the adaptations cannot be accepted. The Registrant is accordingly requested to submit the information for those endpoints performed with the registered substance.

The technical dossier contained statements for the use of a read-across approach from a supporting substance (structural or analogue surrogate) for the registered substance for the endpoint on:

g. Toxicokinetics assessment (Annex VIII, 8.8.1)

Annex XI, section 1.5, sets out the general rules for adaptation of the standard testing regime when grouping of substances and read-across approach is used.

The Registrant has submitted a summary of the use of HBED in clinical trials and states that the studies can be applied to FeHBED because "the iron overload takes place in the process of Fe chelation by HBED and finally product is FeHBED". In addition, six studies conducted with the NaHBED has been submitted. The studies are not toxicokinetic studies. No information on the structure and possible similarity of HBED to the registered substance has been submitted.

The waiving justification provided by the Registrant does not meet the conditions for grouping of substances and read-across approach as set out in Annex XI, section 1.5.

Therefore, the Registrant is required to submit a Toxicokinetics assessment.

2) Missing information related to Chemical Safety Report (CSR)

a. Identification of DNEL(s), (Annex I, 1.4.), and
b. Identification of the PNEC, (Annex I, 3.3.1.)

Articles 10(b) and 14(1) of the REACH Regulation require that the technical dossier for all substances subject to registration in quantities of 10 tonnes or more per year per registrant shall include a Chemical Safety Report in the format specified in Annex I to the REACH Regulation. According to Annex I, 1.0.1. and Annex I, 3.0.1., the objectives of the human health hazard assessment and of the environmental hazard assessment are to derive levels of exposure to the substance above which humans should not be exposed, i.e. DNELs, and to identify the concentration of the substance below which adverse effects in the environmental sphere of concern are not expected to occur, i.e. PNECs, respectively. The obligation to identify DNELs follows from Annex I, 1.4.1. and to derive PNECs from Annex, I, 3.3.1. These values are missing in sections 5.11 and 7.1.2.1 of the Chemical Safety Report. Negative findings in the relevant toxicity or ecotoxicity studies do not constitute sufficient justifications to dismiss the establishment of DNELs and PNECs. The Registrant is accordingly requested to derive DNELs and to calculate PNECs for the aquatic compartment.

c. PBT assessment, (Annex I, section 4),

The Registrant has not provided a PBT and vPvB assessment in the Chemical Safety Report (CSR).

Pursuant to Article 14(3)(d) and Annex I section 0.6 of the REACH Regulation a chemical safety assessment shall include a persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) assessment. Based on the information in the dossier (IUCLID section 5.1 and 5.2), the substance should be considered as P - vP.

Therefore, the Registrant is requested to provide in his CSR a PBT and vPvB assessment

d. The estimated exposure (Exposure scenario and exposure estimation), and the risk characterisation for human health and environment (Annex I sections 5 and 6)

The exposure assessment and risk characterisation are not present in the Chemical Safety Report.

Pursuant to Article 14(4) and Annex I sections 0.6 of the REACH Regulation, if the registrant concludes that the registered substance meets the criteria for classification as dangerous in accordance with Directive 67/548/EEC or is assessed to be persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) he shall include for all identified uses an exposure assessment and a risk characterisation as part of the CSR. As from 1 December 2010 the same obligation applies if the conditions of Article 58(1) of Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation) are met.

In the technical dossier and the CSR the Registrant has classified the substance as dangerous in accordance with Directive 67/548/EEC. Accordingly, pursuant to the provisions quoted above, the Registrant is required to generate in his CSR an exposure assessment and a risk characterisation.

The exposure assessment should be performed in accordance with the principles set out in point 5 of Annex I of the REACH Regulation and in particular provide exposure scenarios and exposure estimations for the registered substance. The exposure assessment should consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the identified hazards.

The risk characterisation should be performed in accordance with the principles set out in point 6 of Annex I of the REACH Regulation. The Registrant should carry out a risk characterisation for each exposure scenario and present it under the relevant heading of the Chemical Safety Report.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds Registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

"Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable."

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. The procedure is described in the Board of Appeal's "Preliminary instructions to Appellants" that can be found at the ECHA website. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]

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