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Safety for the user of the feed additive consisting of ferric citrate chelate (CI-FER™) for suckling and weaned piglets and minor porcine species (Akeso Biomedical, Inc.)

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Abstract

Following a request from the European Commission (EC), the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP Panel) was asked to deliver a scientific opinion on the safety for the users of the feed additive consisting of ferric citrate chelate (CI-FER™) when used as a zootechnical additive for suckling and weaned piglets and minor porcine species. The EC request follows a previous opinion of the FEEDAP Panel. In that opinion, the Panel identified several risks for the users of the additive; it was listed that it posed a risk to users by inhalation, should be considered as an irritant to skin, eyes and mucous membranes, and also that, due to its nickel content, should be considered as a dermal and respiratory sensitiser. The applicant provided additional data including information on the manufacturing process of the additive and data supporting the safety of the additive for the users to address those concerns. Some changes have been applied to the original manufacturing process which led to a dust-free additive, with the following specifications: total iron $\leq$ 23%, iron (III) $\geq$ 16.5% and moisture $\leq$ 10.0%. The FEEDAP Panel concluded that CI-FER™ does not pose a risk by inhalation and is classified as non-irritant to the skin. The additive should be classified as a skin sensitiser. In the absence of new data, the FEEDAP Panel reiterates its previous conclusion that the additive should be considered irritant to eyes.

Keywords: zootechnical additives, gut flora stabiliser, CI-FER™, ferric citrate chelate, safety, users

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

Regulation (EC) No 1831/2003 establishes rules governing the Community authorisation of additives for animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant, Akeso Biomedical Inc. USA, represented in EU by Pen & Tec Consulting SLU, is seeking a Community authorisation of Ferric Citrate Chelate as a feed additive to be used as gut flora stabiliser and other zootechnical additive for piglets (suckling and weaned) (Table 1).

Table 1: Description of the substances

Category of additive	Zootechnical additives
Functional group of additive	Gut and flora stabilisers and other zootechnical additives
Description	Ferric Citrate Chelate for piglets (suckling and weaned) and minor porcine species
Target animal category	Piglets (suckling and weaned) and minor porcine species
Applicant	Akeso Biomedical, Inc. USA, represented in the EU by Pen & Tec Consulting SLU
Type of request	New opinion

On 28 November 2019, the Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority ("Authority"), in its opinion on the safety and efficacy of the product, identified several risks for the users of the additive.

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment and to allow a revision of Authority's opinion. The new data have been received on 20 March 2020 and 2 April 2020.

In view of the above, the Commission asks the Authority to deliver a new opinion on Ferric citrate chelate as a feed additive for piglets (suckling and weaned) and minor porcine species based on the additional data submitted by the applicant.

1.2. Additional information

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) adopted in 2019 an opinion on the safety and efficacy of the preparation of ferric citrate chelate (CI-FER™) as a feed additive for piglets (weaned, suckling) and minor porcine species (EFSA FEEDAP Panel, 2019). In that opinion, the FEEDAP Panel identified several risks for the users of the additive. The applicant has provided additional data to address these concerns.

The product has not been authorised in the European Union (EU) as a feed additive.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information[1] to a previous application of the same product.[2]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety for user of ferric citrate chelate (CI-FER™) is in line with the principles laid down in Regulation (EC) No 429/2008[3] and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers

[1] FEED dossier reference: FAD-2020-0032.
[2] FEED dossier reference: FAD-2018-0065.
[3] Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

(EFSA FEEDAP Panel, 2012), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017).

3. Assessment

The additive ferric citrate chelate (CI-FER™) consists of ferric citrate chelate. It is proposed to be used as a zootechnical additive (functional groups: gut flora stabiliser, other zootechnical additives). The additive is intended to be used in feed for suckling and weaned piglets and minor porcine species at the same physiological stage at a minimum level of 500 mg additive/kg of complete feed. For the purpose of this scientific opinion, the additive will be referred to as CI-FER™.

In a previous opinion of the FEEDAP Panel on the same additive (EFSA FEEDAP Panel, 2019), the FEEDAP Panel concluded that CI-FER™ posed a risk to users by inhalation and should be considered irritant to skin, eyes and mucous membranes, and also that, due to its nickel content, should be considered a dermal and respiratory sensitiser.

The applicant has submitted additional information related to the characterisation, manufacturing process and the safety of the additive for the users and this new information is the subject of this opinion.

3.1. Characterisation of the additive and manufacturing process

The additive was characterised in the previous opinion of the FEEDAP Panel as follows: it contains by specification a maximum of 3.0% Fe(II), Fe(III) in the range of 16.5–20.0% and a maximum of 27.0% of water (EFSA FEEDAP Panel, 2019). The applicant has reported that the manufacturing process of the additive has been optimised to improve the ferric citrate yield and to achieve a dust-free additive. Following the updates in the manufacturing process the applicant proposes new specifications for the composition of the additive (listed below), as well as for maximum content of nickel (50 mg/kg); furthermore, the dusting potential has been reduced[4,5] from 9 g/m^3 to 0 g/m^3.

The applicant submitted information on the new manufacturing process,[6] including the modifications that were introduced[5]:

- [redacted]
- Oil (0.5% w/w) is introduced during final drying to reduce the dust of the final additive to zero. Although the data provided on the composition and physical properties of the additive has been obtained from several batches produced with the addition of 0.5% (w/w) coconut oil, the applicant stated that other suitable oils (e.g. soya oil) could be used.

The applicant has proposed new specifications for the additive: total iron ≤ 23%, Iron(III) ≥ 16.5% and moisture ≤ 10.0%; the contents of Iron(II) and citrate are not defined in the specifications.[7] The analysis of three batches prepared with the addition of 0.5% (w/w) coconut oil showed compliance with these specifications[7]: total iron 17.6% (17.4–17.7%), Iron(III) 17.4% (17.2–17.5%), moisture 8.5% (8.5–8.6%). Average content of iron(II) was 0.2% (all three batches) and of citrate 68.4% (68.4–68.5%). The FEEDAP Panel notes that, approximately, 5.3% of the additive remains unidentified. The applicant provided also analytical data of five additional batches manufactured without the coconut oil[7]; the results also showed compliance with these specifications.

The concentrations of undesirable substances were analysed in the same five batches of the oil-free additive as the main component's batch to batch variation. The analysis of heavy metals (cadmium Cd, mercury Hg and lead Pb), arsenic (As) and fluorine (F) resulted in the following ranges: Cd < 0.005–0.025 mg/kg, Hg < 0.009–0.05 mg/kg, Pb 0.045–0.299 mg/kg, As < 0.025 mg/kg and F < 5 mg/kg.[8] The levels of dioxins and the sum of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F) and dioxin-like polychlorinated biphenyls (PCBs) were 0.07–0.101 ng WHO-PCDD/F-TEQ/kg

[4] Technical Dossier/Enclosure_6_CoAs.
[5] Technical Dossier/Supplementary Information October 2020.
[6] Technical Dossier/Enclosure_4_New_Annex_II_3_2_1_Conf.
[7] Technical Dossier/Supplementary Information October 2020/Enclosure_5.
[8] Values preceded by the symbol "<" refer to the limit of quantification (LOQ) of the analytical method.

and 0.07–0.104 ng WHO-PCDD/F-PCB-TEQ/kg, respectively. The concentrations of the undesirable substances analysed comply with those set in Directive 2002/32/EC[9] for compounds of trace elements or, when not mentioned in the Directive, do not represent a safety concern. Nickel content, analysed in the three batches manufactured with the coconut oil, was found in the range of 20.0–20.4 mg/kg.

Levels of microbial impurities and aflatoxin B1, analysed in the same five batches of the oil-free additive used for the batch-to-batch variation, showed compliance with the specifications: aerobic plate counts $\leq 2 \times 10^3$ CFU/g, total coliforms not detected in 1 g, *Salmonella* spp. not detected in 25 g, *Escherichia coli* ≤ 10 CFU/g, yeast and moulds ≤ 200 CFU/g; aflatoxin B1 < 10 μg/kg.

The FEEDAP Panel acknowledges that most of the impurities of the additive were analysed in the additive without the addition of 0.5% (w/w) coconut oil but considers that the addition of any vegetable oil compliant with the Directive 2002/32/EC on undesirable substances would not significantly impact in the content of impurities.

The product is an orange–brown powder. The applicant provided data on dusting potential of three batches of the additive and analysed by the Stauber–Heubach method,[10] which showed that the product was dust free.

3.2. Safety for the users

In the previous opinion, the FEEDAP Panel concluded that 'users may be exposed to iron and nickel from the additive by inhalation at levels exceeding the threshold limit value TLV/OEL[11] values by at least three and one orders of magnitude, respectively. The FEEDAP Panel considers that the compound under assessment poses a risk to users by inhalation. The product should also be considered as an irritant to skin, eyes and mucous membranes. Due to the presence of nickel, CI-FER™ should also be considered as a dermal and respiratory sensitiser' (EFSA FEEDAP Panel, 2019).

The applicant has submitted new information/studies on the effects of the additive on the respiratory system and on the skin, which are described below.

3.2.1. Effects on the respiratory system

With the changes in the manufacturing process, the formulated additive is dust-free. Therefore, there is no exposure, and thus no risk to users by inhalation.

3.2.2. Effects on the skin and eyes

The applicant provided an *in vitro* skin irritation study with CI-FER™ (oil-free preparation), using a commercial reconstructed human epidermis (RhE) model named EPISKIN™.[12] The study was GLP compliant and was performed according to the OECD Guideline Test No. 439 '*In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method'.[13] Based on the results obtained, the test item CI-FER™ is classified as non-irritant to the skin (UN GHS[14] No Category).

In the current dossier, no data on the effects of the additive to eyes were submitted.

The nickel content of the additive is up to 20.4 mg/kg; given its well-known sensitisation potential (EC, 2011) and in the absence of skin sensitisation studies, the additive should be considered a skin sensitiser.

3.2.3. Conclusions on the safety for the users

CI-FER™ does not pose a risk by inhalation and it is classified as non-irritant to the skin. The additive should be classified as a skin sensitiser. In the absence of new data, the FEEDAP Panel reiterates its previous conclusion that the additive should be considered an eye irritant.

[9] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 10.
[10] Technical Dossier/Supplementary Information/Enclosure 16, Annex II 1 5 7 SH.
[11] TLV: Threshold limit value. OEL: Occupational exposure limit.
[12] Technical dossier/Enclosure_5_Annex_III_3_1_2.
[13] Guideline version adopted on 18 July 2019. Available online: https://www.oecd-ilibrary.org/environment/test-no-439-in-vitro-skin-irritation-reconstructed-human-epidermis-test-method_9789264242845-en
[14] United Nations Global Harmonised System.

4. Conclusions

Based on the new information provided on the manufacturing process of the additive, the relative data on characterisation and the further data supporting the safety for the users, the FEEDAP Panel concludes that CI-FER™ does not pose a risk by inhalation, is not irritant to the skin, but should be considered an eye irritant and a skin sensitiser.

5. Documentation as provided to EFSA/Chronology

Date	Event
29/04/2020	Dossier received by EFSA. Ferric citrate chelate for piglets (weaned, suckling) and minor porcine species. Submitted by Akeso Biomedical Inc.
29/04/2020	Reception mandate from the European Commission
15/05/2020	Application validated by EFSA – Start of the scientific assessment
14/07/2020	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. *Issues: characterisation, safety for the users.*
28/10/2020	Reception of supplementary information from the applicant - Scientific assessment re-started. Clarifications received by e-mail (25.11.2020).
27/01/2021	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

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Abbreviations

CFU	colony forming units
FEEDAP	EFSA Panel on Additives and Products or Substances used in Animal Feed
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PCB	polychlorinated biphenyl
PCDD/F	polychlorinated dibenzo-*p*-dioxins and dibenzofurans
RhE	reconstructed human epidermis
TEQ	toxic equivalents
TLV	threshold limit value
UN GHS	United Nations Global Harmonised System
WHO	World Health Organization