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Safety and efficacy of iron compounds (E1) as feed additives for all species: ferric oxide based on a dossier submitted by Poortershaven Industriële Mineralen B.V.

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

Abstract

The additive under assessment, ferric oxide, contains between 57% and 69% iron (Fe). The EFSA FEEDAP Panel could not conclude on the safety of ferric oxide for the target animals owing to that (i) the application of ferric oxide red is for all animal species, (ii) lifetime administration to animals is not excluded and (iii) a sufficient biological and toxicological database was not available. Regarding (i) the very low absorption of iron from the ferric oxide by target animals and (ii) the homoeostatic regulation of iron metabolism in animals, any influence of feeding the ferric oxide on the iron content of edible tissues and products is not expected. The use of ferric oxide in animal nutrition is unlikely to result in a direct exposure of the consumer to this oxide. Consequently, the supplementation of feed for food-producing animals with ferric oxide would likely not constitute a risk to consumers. Ferric oxide is an irritant to skin and eyes by mechanical action. Owing to the nickel content in the additive, the ferric oxide should be regarded as dermal and respiratory sensitiser. Inhalation of ferric oxide, and the contained chromium and nickel, is a hazard; as exposure by inhalation is likely, handling ferric oxide would be a risk for the users. As there is concern about the possible genotoxicity of ferric oxide, any route of exposure should be considered as hazardous. Iron oxides are ubiquitous in the environment. Any additional input from the nutritional use of ferric oxide in food-producing animals is considered negligible. It is unlikely that the use of the additive in animal nutrition would pose a risk to the environment. Ferric oxide should not be considered as iron source capable to meet iron requirements of animals.

Keywords: nutritional additive, compounds of trace elements, iron, ferric oxide, safety, environment, efficacy

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Summary

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on safety and efficacy of ferric oxide as feed additive for all animal species.

Three manufacturing routes are described for ferric oxide: mining, synthetic and derusting. It contains between 57% and 66% (mining), 68% (synthetic) and 69% (derusting) iron (Fe).

The FEEDAP Panel could not conclude on the safety of ferric oxide for the target animals owing to that (i) the application of ferric oxide red is for all animal species, (ii) lifetime administration to animals is not excluded and (iii) a sufficient biological and toxicological database was not available.

Regarding (i) the very low absorption of iron from the ferric oxide by target animals and (ii) the homoeostatic regulation of iron metabolism in animals, any influence of feeding the ferric oxide on the iron content of edible tissues and products is not expected. The use of ferric oxide in animal nutrition is unlikely to result in a direct exposure of the consumer to this oxide. Consequently, the supplementation of feed for food-producing animals with ferric oxide would likely not constitute a risk to consumers.

Ferric oxide is an irritant to skin and eyes by mechanical action. Owing to the nickel content in the additive, the ferric oxide should be regarded as dermal and respiratory sensitiser. Inhalation of ferric oxide, and the contained chromium and nickel, is a hazard; as exposure by inhalation is likely, handling ferric oxide would be a risk for the users. As there is concern about the possible genotoxicity of ferric oxide, any route of exposure should be considered as hazardous.

Iron oxides are ubiquitous in the environment. Any additional input from the nutritional use of ferric oxide in food-producing animals is considered negligible. It is unlikely that the use of the additive in animal nutrition would pose a risk to the environment.

Ferric oxide should not be considered as iron source capable to meet iron requirements of animals.

The FEEDAP Panel made some recommendations concerning the denomination of the additive and its specifications.

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 10(2) of that Regulation also specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, at the latest 1 year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of 7 years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission (EC) received a request from Poortershaven Industriële Mineralen B.V.[2] for re-evaluation of the authorisation of the iron-containing additive, ferric oxide, when used as a feed additive for all animal species (category: nutritional additive; functional group: compound of trace elements).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 24 May 2012.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment, and on the efficacy of 'Ferric oxide', when used under the proposed conditions of use (see Section 3.1.2).

1.2. Additional information

Iron (Fe) is the most abundant trace element in mammals. It serves as a constituent in proteins (e.g. haemoproteins: haemoglobin, myoglobin; non-haemoproteins: ferritin, transferrin) and as a cofactor for many important iron-dependent enzymes (e.g. cytochromes A, B, C; peroxidases, catalases). Haemoglobin makes up 70% of the entire iron body pool. The intestinal absorption of iron and its retention is highly regulated via homeostasis (for reviews see Wessling-Resnick, 2000; Miret et al., 2003; Fuqua et al., 2012). Iron is present in biological systems in one of the two oxidation states, and redox interconversions of the ferrous (Fe(II)) and ferric (Fe(III)) forms are central to the biological properties of this trace element. Aerobic metabolism depends on iron. As a constituent of haemoglobin, it is involved in oxygen and carbon dioxide transport. It plays a central role as cofactor for most of the enzymes of the Krebs cycle and functions as electron carrier (McDowell, 2003; Suttle, 2010; Ponka et al., 2015).

The additive 'Ferric oxide' had been authorised in the European Union (EU) under the element Iron-Fe for all animal species 'Without a time limit' (Commission Regulation (EC) No 1334/2003[3] and amendments, and Commission Regulation (EC) No 479/2006)[4]. Following the provisions of Article 10 (1) of Regulation (EC) No 1831/2003, the compound was included in the EU Register of Feed Additives under the category 'Nutritional additives' and the functional group 'Compounds of trace elements'.[5]

EFSA issued an opinion on the safety of the chelated forms of iron, copper, manganese and zinc with synthetic feed grade glycine (EFSA, 2005). In the frame of re-evaluation, EFSA has delivered five opinions on iron-based additives: iron chelate of amino acids, hydrate (EFSA FEEDAP Panel, 2013, 2016a); ferrous sulfate, heptahydrate (EFSA FEEDAP Panel, 2014a, 2016a); ferrous sulfate, monohydrate (EFSA FEEDAP Panel, 2014b, 2016a); ferrous carbonate (EFSA FEEDAP Panel, 2015,

[1] Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.
[2] Poortershaven Industriële Mineralen, B.V. Wijnhaven 84, 3011 WT, Rotterdam, The Netherlands.
[3] Commission Regulation (EC) No 1334/2003 of 25 July 2003 amending the conditions for authorisation of a number of additives in feedingstuffs belonging to the group of trace elements. OJ L 187, 26.7.2003, p. 11.
[4] Commission Regulation (EC) No 479/2006 of 23 March 2006 as regards the authorisation of certain additives belonging to the group compounds of trace elements. OJ L 86, 24.3.2006, p. 4.
[5] European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. http://ec.europa.eu/food/food/animalnutrition/feedadditives/comm_register_feed_additives_1831-03.pdf

2016a); ferric chloride, hexahydrate, ferrous fumarate, and ferrous chelate of glycine, hydrate (EFSA FEEDAP Panel, 2016a).

In 2015, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) adopted a scientific opinion on the re-evaluation of iron oxides and hydroxides (E 172) as food additives (EFSA ANS Panel, 2015). Following that, the FEEDAP Panel adopted a scientific opinion on the safety and efficacy of iron oxide black, red and yellow for all animal species as colourings in feed (EFSA FEEDAP Panel, 2016b).

A compilation of risk assessments carried out on iron and its compounds, including opinions from EFSA Panels other than the FEEDAP Panel, is in Appendix A. A list of authorisations of iron compounds in the EU, other than as feed additives, is reported in Appendix B.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of ferric oxide as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003 Regulation (EC) No 429/2008[7] and the applicable EFSA guidance documents.

The FEEDAP Panel used the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, scientific papers and other scientific reports to deliver the present output.

EFSA commissioned the University of Gent (Belgium) to carry out a study on the biological role, content in feed and requirements in animal nutrition of selected trace and ultratrace elements, including iron. The findings were submitted to EFSA in the form of a technical report (Van Paemel et al., 2010). Information from this report has been used in this opinion.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of iron (eight compounds, including ferric oxide) in animal feed. The Executive Summary of the EURL report can be found in Annex A.[8]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of ferric oxide is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance on nutritional additives (EFSA FEEDAP Panel, 2012a), Technical guidance: Tolerance and efficacy studies in target animals (EFSA, 2011), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008a), Guidance for the preparation of dossiers for the re-evaluation of certain additives already authorised under Directive 70/524/EEC (EFSA, 2008b), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012c), and Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d).

3. Assessment

The opinion is based on data provided by a company involved in the production/distribution of ferric oxide and publicly available literature. In particular, the Opinion on the re-evaluation of iron oxides and hydroxides (E 172) as food additives (EFSA ANS Panel, 2015) and the Opinions on iron-based feed additives (EFSA FEEDAP Panel, 2013, 2014a,b, 2015, 2016a) and on iron oxide black, red and yellow as colourings in feed (EFSA FEEDAP Panel, 2016b) were considered.

It should be recognised that these data cover only a fraction of the ferric oxide placed on the market as compound of trace element.

[6] FEED dossier reference: FAD-2010-0236.

[7] 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.

[8] The full report is available on the EURL website: https://ec.europa.eu/jrc/sites/default/files/FinRep-SANCO-Iron.pdf

3.1. Characterisation

For compounds of trace elements, the element itself is considered the active substance.

3.1.1. Ferric oxide

3.1.1.1. Identity of the additive

'Ferric oxide' (Chemical Abstracts Service (CAS) no 1309-37-1) has the chemical formula Fe_2O_3 (molecular weight 159.69 Da; theoretical iron content 69.6%). It is a red brown powder.

Other chemical names are iron sesquioxide, anhydrous ferric oxide, and anhydrous iron (III) oxide. Synonyms for ferric oxide as colourant (iron oxide red): CI Pigment Red 101; CI (1975) No 77491; INS No 172(ii). Other names: hematite, ferric iron, red iron oxide, rouge, maghemite, colcothar, rust, ochre.

The applicant stated that iron oxides are on the market under different names and references. The information given in the first data set referred to 13 different products, named with in-house identifiers.[9] In a supplementary information data set submitted to EFSA,[10] the applicant clarified that these products could be assigned to each of four groups, three of them based on their origin and manufacturing process (Group A – products obtained through extraction from nature; Group B – products made synthetically from iron flakes; and Group C – products made from derusting) and one which was composed of products blends of different iron oxides. Further to that, the applicant submitted an amended Section II of the Dossier 'Identity, characterisation and conditions of use of the additive; methods of analysis' in which the products to be assessed were reduced to five, allocated to the groups defined above as follows[11]: Group A ('A1'/'A2'/'A3'), Group B ('B') and Group C ('C'). The products are presented as a red brown powder, odourless; they are insoluble in water.[12]

Products obtained by extraction from natural sources

This group initially included the products 'A1', 'A2' and 'A3'. After an in-depth examination of the data submitted, and the request for clarification to the applicant, it was identified that there were two manufacturing processes for the iron oxides of group A. One of them starting from dry ore and subsequently crushed and milled results in the 'iron oxide red' (Fe_2O_3) subject of re-evaluation (products 'A1' and 'A2').[13] Product 'A3' is derived from another manufacturing process starting with a slurry from natural iron ores, and giving 'iron oxide black' ($FeO{\cdot}Fe_2O_3$). Therefore, only products 'A1' and 'A2' will be characterised below.

Concerning the iron and ferric oxide content of these products, the specifications provided were $\geq$ 55% and $\geq$ 76%, respectively, for 'A1'[14] and $\geq$ 64.5% and $\geq$ 93%, respectively, for 'A2'.[15] Analytical data on total iron content determined by an X-Ray fluorescence (XRF) resulted in 56.6% and 65.9% as average of five and three batches for 'A1' and 'A2', respectively.[16] Further to that, the content of ferrous oxide was determined in one batch of each product with the analysis of the iron(II) in the products by a potentiometric titration, giving the values of 0.45% and 0.55% for 'A1' and 'A2', respectively; from the total iron content, the content of ferric oxide was calculated to be 76.8% and 92.89% in the 'A1' and 'A2', respectively.[17]

Levels of heavy metals (cadmium (Cd), lead (Pb), mercury (Hg)), arsenic (As) and fluorine (F), were analysed in one to four batches each of the two products. For the product 'A1', the following results were reported (in mg/kg)[18]: Cd (three batches) < 0.01–< 0.10, Pb (four batches) 5.5–13, Hg (three batches) 0.02–0.74, As (four batches) 6.1–14 and F (two batches) 48–234. For the product, 'A2' the following results were reported (in mg/kg)[19]: Cd (three batches) 0.03–< 0.10, Pb (three batches) 3.4–4.3, Hg (three batches) 0.04–< 0.10, As (three batches) 0.15–3.54 and F (one batch) 38. These

[9] Technical Dossier/Section II.
[10] Technical Dossier/Supplementary Information January 2013.
[11] Corresponding to the following products, based on the in-house identifiers described in the Technical dossier: 'A1' to P5 (or 5P), 'A2' to S2-600, 'A3' to NM400; 'B' to P3B (or P3S); 'C' to BT98 (or bt98).
[12] Technical Dossier/Supplementary Information March 2014.
[13] Technical Dossier/Supplementary Information March 2015. 1.1 Flow.Chart.P5.S2.600.FeCO3.Range3.pdf.
[14] Technical Dossier/Supplementary Information June 2015/Annex 3.3.
[15] Technical Dossier/Supplementary Information June 2015/Annex 3.4.
[16] Technical Dossier/Supplementary Information March 2014/Section_2_Fe2O3 140313.pdf. Technical Dossier/Supplementary Information March 2015.
[17] Technical Dossier/Supplementary Information June 2015/Annex 1.
[18] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.a.
[19] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.b.

values comply with the thresholds set in Directive 2002/32/EC[20] for compounds of trace elements or, if not mentioned in the Directive, do not appear to represent a safety concern. The nickel content (three batches each of product 'A1' and 'A2') showed an average of 9 and 67 mg/kg for 'A1' and 'A2', respectively.[21]

Dioxins and the sum of dioxins plus dioxin-like polychlorinated biphenyls (PCBs) were analysed each in three and one batches of 'A1' and 'A2', showing 0.018–0.07 and 0.025–0.17 ng WHO-PCDD/F-TEQ/kg 'A1' and 'A2', respectively, and 0.003 and 0.19 ng WHO-PCDD/F-PCB-TEQ/kg 'A1' and 'A2', respectively[22]; these concentrations comply with those set in Directive 2002/32/EC.

In total, it appeared that the product 'A1' has a lower purity than the 'A2'; the applicant stated that the two products originate from two different ores, being that the reason for the different composition and physical properties (e.g. loss in ignition: 8% for 'A1'[23] and 0.7% for 'A2').[24] For products 'A1' and 'A2', bulk density was determined to be 0.95 and 1.40 g/cm^3, respectively, and density 4.4 and 5.0 kg/L, respectively.[25]

Particle size distribution, giving the required dimensions, was measured by sieving one batch of the product 'A1'[25] and four batches of product 'A2'.[26] Both products showed 100% (w/w) of the particles below 50 μm, while the amount below 10 μm was 95% (w/w) in four out of five batches. Dusting potential (Stauber–Heubach method), measured in three batches each of product 'A1' and 'A2', ranged from 0.3 to 0.5 g/m^3 for 'A1' and from 0.2 to 1.0 g/m^3 for 'A2'.[27]

Product obtained by synthesis

The product 'B' is produced by synthesis from iron flakes.

For the production of iron oxide 'B', preparations of ferrous sulfate and ferrous nitrate are oxidised under steam. The wet material is filtered, rinsed, dried and sieved. The resulting product is the pigment iron oxide red identical to the ferric oxide, subject of the current re-evaluation.[12,28]

Concerning the iron and ferric oxide content of 'B', the specifications provided were ≥ 67% and ≥ 95.5%, respectively.[29] Analytical data on total iron content determined by an XRF resulted in 68.0% as average of five batches; the calculated amount of ferric oxide was 97.2%.[30]

Levels of heavy metals (Cd, Pb, Hg), As and F, were analysed in two to three batches of the product. The following results were reported (in mg/kg)[31]: Cd (three batches) 0.01–< 0.10, Pb (three batches) 0.16–9.16, Hg (three batches) 0.01–< 0.10, As (three batches) 0.44–7.71 and F (two batches) 6.9–40. These values comply with the thresholds set in Directive 2002/32/EC for compounds of trace elements or, if not mentioned in the Directive, do not represent a safety concern. The nickel content measured in one batch was 25 mg/kg.[32]

Dioxins and the sum of dioxins plus dioxin-like PCBs were analysed each in two and one batches of the product, showing 0.024–0.028 ng WHO-PCDD/F-TEQ/kg B and 0.003 and 0.061 ng WHO-PCDD/F-PCB-TEQ/kg 'B', respectively[33]; these concentrations comply with those set in Directive 2002/32/EC.

The bulk density was determined to be 0.80 g/cm^3 and density 5.0 kg/L.[25]

Particle size distribution was measured by sieving in three batches of the product 'B'[34] showing 100% (w/w) of the particles below 10 μm. Dusting potential (Stauber–Heubach method) measured in three batches ranged from 0.2 to 0.5 g/m^3.[35]

[20] 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.
[21] Technical Dossier/Supplementary Information March 2015/Annexes 4.1–4.6.
[22] Technical Dossier/Supplementary Information March 2014/Annexes 2.1.4.f., 2.1.4.g. 2.1.4.h. and 2.1.4.i.
[23] Technical Dossier/Supplementary Information March 2015/Annex 2.1.3.b.
[24] Technical Dossier/Supplementary Information March 2015/Annex 2.1.3.d.
[25] Technical Dossier/Supplementary Information March 2014/Annex 2.1.5.a.
[26] Technical Dossier/Supplementary Information March 2014/Annexes 2.1.5.a. and 2.1.5.b.
[27] Technical Dossier/Supplementary Information March 2015/Annexes 4.7–4.12.
[28] As reported by the applicant, the manufacturing process could also provide the product ZBLM, an iron oxide yellow ($FeO(OH)\cdot H_2O$, CAS number 51274-00-1, MW: 88.85 (FeO(OH)).
[29] Technical Dossier/Supplementary Information June 2015/Annex 3.2.
[30] Technical Dossier/Supplementary Information March 2014/Section_2_Fe2O3 140313.pdf (Annex 2.1.3.h.). Technical Dossier/Supplementary Information March 2015.
[31] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.c.
[32] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.e.
[33] Technical Dossier/Supplementary Information March 2014/Annexes 2.1.4.k. and 2.1.4.l.
[34] Technical Dossier/Supplementary Information March 2014/Annex 2.1.5.d.
[35] Technical Dossier/Supplementary Information March 2014/Annex 2.4.3.c.

Product obtained by derusting

The product 'C' is made from derusting. This iron source is then mixed with hydrochloric acid and heated in a furnace under a stream of air. The hydrochloric acid is recycled and the resulting iron oxide is stored.[12]

Concerning the iron and ferric oxide content of 'C', the specifications provided were ≥ 69% and ≥ 98.3%, respectively.[36] Analytical data on total iron content determined by an XRF resulted in 69.2% as average of five batches; the calculated amount of ferric oxide was 99.3%.[37]

Levels of heavy metals (Cd, Pb, Hg), As and F, were analysed in two to five batches of the product. The following results were reported (in mg/kg)[38]: Cd (five batches) < 0.01–< 0.10, Pb (five batches) 0.62–< 1.00, Hg (five batches) < 0.01–< 0.10, As (five batches) 0.03–0.53 and F (two batches) < 5–35. These values comply with the thresholds set in Directive 2002/32/EC for compounds of trace elements or, if not mentioned in the Directive, do not represent a safety concern. The nickel and chromium content (three batches) showed an average of 107 mg/kg and 404 mg/kg, respectively.[39]

Dioxins and the sum of dioxins plus dioxin-like PCBs were analysed each in four and two batches of the product, showing 0.04–0.11 ng WHO-PCDD/F-TEQ/kg 'C' and 0.063–0.12 ng WHO-PCDD/F-PCB-TEQ/kg 'C', respectively[40]; these concentrations comply with those set in Directive 2002/32/EC.

Particle size distribution was measured by sieving in three batches of the product 'C'[41] showing 100% (w/w) of the particles below 150 μm, and an average of 95.7% below 35 μm. Further, three batches were examined for particle size distribution by a laser diffraction and the results provided were on an average 57% (v/v) of particles below 50 μm and 25% (v/v) below 10 μm.[42] Dusting potential (Stauber–Heubach method) measured in two batches was 0.4 and 2.7 g/m^3.[43]

The FEEDAP Panel notes that all particle size determinations, with the exception of three batches of product 'C', were performed by a sieve analysis. The lowest particle size by this method is determined by the availability of sieves with a certain diameter, particles below 10 μm cannot be separated in further fractions. With a laser diffraction method, the micronised fraction can be measured (from above 100 to below 1,000 nm). It varied for the three batches of 'C' between 2.2% and 3.7% (v/v). No more data on the micronised fraction were available and no data at all would give information on a potential nanofraction.

3.1.1.2. Stability and homogeneity

No stability data are required for inorganic compounds of trace elements.

No experimental data on homogenous distribution of the additive were provided.

3.1.2. Physicochemical incompatibilities in feed

According to the current knowledge, no incompatibilities resulting from the use of ferric oxide in compound feed are expected, other than those widely known and considered by feed manufacturers in diet formulation.

3.1.3. Conditions of use

The iron compound under application, ferric oxide, is intended to supply iron in final feed for all animal species/categories up to a maximum total content of 250 mg/day for piglets up to 1 week before weaning,[44] 750 mg/kg complete feedingstuffs for other pigs, 500 mg/kg complete feedingstuffs for ovines, 1,250 mg/kg complete feedingstuffs for pets and 750 mg/kg complete feedingstuffs for other animal species.

[36] Technical Dossier/Supplementary Information June 2015/Annex 3.1.
[37] Technical Dossier/Supplementary Information March 2014/Section_2_Fe2O3 140313.pdf (Annex 2.1.3.i.). Technical Dossier/Supplementary Information March 2015.
[38] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.d.
[39] Technical Dossier/Supplementary Information March 2015/Annexes 6.1 to 6.3.
[40] Technical Dossier/Supplementary Information March 2014/Annex 2.1.4.m.
[41] Technical Dossier/Supplementary Information March 2014/Annex 2.1.5.c.
[42] Technical Dossier/Supplementary Information March 2015/Annexes 5.3–5.5.
[43] Technical Dossier/Supplementary Information March 2015/Annexes 5.1 and 5.2.
[44] It is noted that the units in the entry for *piglets up to 1 week before weaning* in the Proposal for Register Entry submitted by the applicant are incorrect: 250 mg/kg complete feedingstuff, instead of 250 mg/day.

3.2. Safety

3.2.1. Toxicological studies

No toxicity studies were produced by the applicant. In its recently published opinion on the safety and efficacy of iron oxides as colourings in animal nutrition, the FEEDAP Panel summarised the toxicology of iron oides (EFSA FEEDAP Panel, 2016b) based on the above mentioned opinion of the ANS Panel (EFSA ANS Panel, 2015). An extract of that opinion, particularly referring to the iron oxide under assessment, is given below.

In 1974, Joint FAO/WHO Expert Committee on Food Additives (JECFA) allocated a 'Temporary ADI not specified' to iron oxides and hydrated iron oxides due to the lack of information on physiological absorption and iron storage following the use of iron oxides as food pigments. At the 1978 JECFA meeting, this temporary acceptable daily intake (ADI) was extended until 1979. In 1980, an ADI of 0–0.5 mg/kg body weight (bw) per day was established (JECFA, 1980).

The available data indicate that absorption of iron from iron oxides is low. In rats, 0.01–2.3% of the total oral dose of microsized red iron oxide (Fe_2O_3) was absorbed and distributed in different organs or excreted in urine. Low absorption of iron (0.01%) from red iron oxide was observed in humans receiving a diet containing red iron oxide, whereas a higher absorption of yellow iron oxide (1.5–2.4% of the dose) was described in similar populations. In these human studies, the addition of ascorbic acid increased by 5–50 times the iron absorption rates from diets containing either red iron oxide (Fe_2O_3) or yellow iron oxide (FeO(OH)). The Panel noted that there are no data regarding the biological fate of microparticles of black iron oxide ($FeO{\cdot}Fe_2O_3$).

Concerning toxicological studies, the Panel noted that there is a lack of information on the presence of nanoparticles in iron oxides used in most of the old studies. Regarding acute toxicity, the available data indicate that iron oxides and hydroxides are of low toxicity in rats and mice.

The subacute oral toxicities of nano red iron oxide (Fe_2O_3-30 nm) and microsized red iron oxide (Fe_2O_3-Bulk) were compared in rats given 0, 30, 300 or 1,000 mg/kg bw per day for 28 days (Kumari et al., 2012). No loss in body weight, no change in feed intake, nor any adverse symptoms and mortality were observed in rats exposed to microsized red iron oxide or to 30 or 300 mg/kg bw per day of red iron oxide nanoparticles. However, rats treated with the high dose of nano red iron oxide (1,000 mg/kg bw per day) showed reduced body weight and feed intake, severe toxic symptoms and several disturbances in biochemical parameters, and adverse histopathological changes in the liver, kidney and spleen. By contrast, microsized red iron oxide did not induce any significant adverse effects in either biochemical parameters or histopathology in rats given the highest dose. This study indicated that the microsized particles, i.e. bulk material, are less potent than the nanoparticles in causing toxicity in the exposed animals. From this study, the Panel identified a no observed adverse effect level (NOAEL) for microsized red iron oxide of 1,000 mg/kg bw per day, the highest dose tested.

No subchronic toxicity studies by oral administration of microsized yellow iron oxide, red iron oxide or black iron oxide were available. A subchronic toxicity of red iron oxide nanoparticles (60–118 nm) was investigated by Yun et al. (2015) in a 13-week oral toxicity study according to the OECD TG 408 (OECD, 1998). Rats received daily doses of 250, 500 or 1,000 mg/kg bw per day for 13 weeks by gavage. Fe_2O_3 nanoparticles had no significant effects on body weight, mean daily food and water consumption when compared to control groups. There were no treatment-related changes in haematological, serum biochemical parameters or histopathological lesions. Some changes observed in organ weights were considered by the authors as not '*toxicologically relevant*'. In blood and all tissues tested, including liver, kidney, spleen, lung and brain, the concentration of Fe showed no dose-associated response in comparison to the control groups. Iron concentrations in the urine of Fe_2O_3 nanoparticle-treated rats showed no significant differences compared to those of control animals. The authors stated that the subchronic oral dosing with Fe_2O_3 nanoparticles showed no systemic toxicity to rats. The Panel agreed with the conclusion of the authors and identified a NOAEL for nanosized red iron oxide of 1,000 mg/kg bw per day, the highest dose tested in rats receiving Fe_2O_3 nanoparticles by gavage. Owing to the presence of nanoparticles in red iron oxide used as food additive, the Panel considered this study as relevant for the assessment of the safety of red iron oxide.

The Panel noted that using similar range of daily doses, adverse effects were observed in rats subacutely treated (28 days) with red iron oxide nanoparticles whilst no effect was described after a subchronic administration (90 days) of such particles to rats. The Panel considered that this difference could be explained by the use of smaller nanoparticles (30 nm) in the subacute study than those used

in the subchronic toxicity study (60–118 nm). The former could be more efficiently available to organs and tissues leading to more severe adverse effects.

Red and black iron oxides, both in nano- and microform (7–30 nm and > 100 nm, respectively), were positive in *in vitro* genotoxicity assays in mammalian cells, where induction of DNA strand breaks and micronuclei was observed. *In vivo* oral administration of both nano- and microsized red iron oxides did not elicit genotoxic effects in rat haemopoietic system, while no data are available for the site-of-contact (gastrointestinal tract). No *in vivo* genotoxicity studies have been performed on black iron oxide and no genotoxicity studies are available for yellow iron oxide. Due to the limitations of the database, and considering the impossibility to read across between iron oxides with different redox state, the Panel considered that the genotoxicity of iron oxides cannot be evaluated based on the available data.

Concerning long-term toxicity and carcinogenicity, no adverse effects were reported in ten dogs maintained from 1 to 9 years on diets containing iron oxide colourant (unspecified compound); the daily consumption was estimated at 428 mg/dog (unpublished study from Carnation Co., 1967, as reported by JECFA, 1983). In a study from Ralston Purina Cat Care Center (1968), no adverse effects were reported in cats maintained on diets containing 1,900 mg/kg diet (475 mg/kg bw per day) of iron from iron oxide (equivalent to 0.27% iron oxide) for periods of 2–9 years. The IARC Monograph (IARC, 1987) stated that there was evidence suggesting lack of carcinogenicity of haematite (red iron oxide) and ferric oxide (unspecified compound) to animals, and that there was inadequate evidence of carcinogenicity in humans.

Concerning reproductive and developmental toxicity, no signs of toxicity were observed in an unpublished study (as reported in JECFA, 1983). However, this study was not available and could not be evaluated by the Panel.

The ANS Panel concluded that an adequate assessment of the safety of E 172 (iron oxides) could not be carried out because a sufficient biological and toxicological database was not available. The ANS Panel concluded also that '*in vivo* genotoxicity data on red iron oxide at the site of contact are absent'.

The FEEDAP Panel expresses in the current opinion its concern on the safety of ferric oxide as compound of trace element as long as such a genotoxicity study is not provided.

3.2.2. Safety for the target species

Before assessing the safety of compounds of iron under application, the FEEDAP Panel made a comparison between the currently authorised maximum iron (total) contents set by Regulation (EC) No 1334/2003, the maximum tolerable levels (MTLs) published by the National Research Council of the USA in 2005 (NRC, 2005) and similar values which could be derived from other more recent publications. The FEEDAP Panel concluded in five scientific opinions on different compounds of iron (EFSA FEEDAP Panel, 2013, 2014a,b, 2015, 2016a) that they are safe when supplied up to a maximum iron content per kilogram complete feedingstuff of 450 mg for bovines and poultry, 500 mg for ovines, 600 mg for pets, and 750 mg for other species/categories, except horses and fish; for piglets up to 1 week before weaning a daily maximum dose of 250 mg Fe is considered safe. Because of insufficient data, the FEEDAP Panel was not in a position to derive a maximum safe iron concentration in feed for horses or fish.

When assessing the ferric oxide red, the compound under assessment, the FEEDAP Panel sees no reason to modify its above conclusions.

No tolerance study was provided to support the safety of ferric oxide for the target species.

The FEEDAP Panel has just adopted an opinion on the safety and efficacy of iron oxide black, red and yellow intended for use as colourings in animal nutrition (EFSA FEEDAP Panel, 2016b). The iron oxide red is chemically identical to the ferric oxide under application. The Panel stated there that

Iron compounds with low water solubility, such as iron oxides, are considered to be inefficient dietary sources of iron (NRC, 1998). In studies in piglets, sheep, calves and chickens with different iron sources, ferric oxide showed negligible or no effects on haematological parameters and/or performance of these animal species (Bell and Tucker, 1963; Ammerman et al., 1967; Willingham and Hill, 1970; Ammerman and Miller, 1972; Cornelius and Harmon, 1976). In rats, 0.01–2.3% of the total oral dose of microsized red iron oxide (Fe_2O_3) was absorbed and distributed in different organs or excreted in urine (EFSA ANS Panel, 2015). Suttle (2010) considered ferric oxide, used as a colouring agent, as being among the poorest of inorganic iron sources although it is capable of impairing copper absorption. It should be noted that ferric oxide has been used as an indigestible marker in digestibility

studies. It is well known that dietary factors modify non-haem iron absorption, e.g. ascorbic acid would increase iron absorption whilst phytate, calcium and polyphenols would decrease (Suttle, 2010). Although the iron status of the organism plays an important role, high iron stores are related to low absorption rates and vice versa.

In the same opinion (EFSA FEEDAP Panel, 2016b), 'the FEEDAP Panel concluded that (i) a substantial absorption of iron oxides as such is not expected; (ii) iron from the iron oxides black, red and yellow will pass the gastrointestinal tract of target animals essentially unchanged, and (iii) iron from the iron oxides will therefore not measurably contribute to the iron metabolism of target animals'. Considering these aspects, iron from ferric oxide would be equally safe as ineffective in meeting the iron demands of animals.

The FEEDAP Panel noted that as (i) the application of ferric oxide red is for all animal species, (ii) lifetime administration to animals is not excluded and (iii) a sufficient biological and toxicological database was not available, no conclusion on the safety of ferric oxide for the target animals could be made.

3.2.3. Safety for the consumer

Regarding (i) the very low absorption of iron from ferric oxide by target animals and (ii) the homoeostatic regulation of iron metabolism in animals, any influence of feeding the ferric oxide on the iron content of edible tissues and products is not expected.

Although there are no data regarding the occurrence and the biological fate of nano- and microparticles of iron oxide, the use of ferric oxide in animal nutrition is unlikely to result in a direct exposure of the consumer to this oxide.

The FEEDAP Panel concludes that the supplementation of feed for food-producing animals with ferric oxide under assessment would likely not constitute a risk to consumers.

3.2.4. Safety for the user

No specific studies were provided by the applicant regarding the toxicity of the additive for the users.

3.2.4.1. Effects on the eyes and skin

Iron oxides are common additives to cosmetic products. They are usually non-toxic, no allergic and, inclusively, a claim that topical iron chelators might represent a novel and simple approach to prevent skin ageing was recently reported (Pouillot et al., 2013).

Mechanical irritation of skin and eyes may occur depending on the particle size.

The nickel content of the additive is up to 107 mg/kg; given its well-known sensitisation potential (European Commission, 2011), it would be prudent to consider the additive as dermal and respiratory sensitiser (Nemery, 1990; Schnabel et al., 2010; Klein and Costa, 2015).

3.2.4.2. Effects on the respiratory system

Taking into consideration the high dusting potential (up to 2.7 g/m^3), exposure of the lungs is likely if the dust is inhaled.

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) noted that epidemiological studies of miners potentially exposed to iron ore dust or iron oxide had an increased risk of developing lung cancer, although it was not clear whether the cancer was caused by exposure to radiation or dust in the mines (WHO-IARC, 1972). Studies in mice, hamsters and guinea pigs showed no increased risk of cancer with inhalatory or intratracheal exposure to iron oxides. The IARC concluded that ferric oxide is not classifiable as to its carcinogenicity to humans (Group 3) (WHO-IARC, 1987).

A limit for occupational exposure of iron oxide of 5 mg/m^3 was recommended by the American Conference of Governmental Industrial Hygienist (ACGIH, 2006). Regarding the high dusting potential of the additive under application, this value may be exceeded by more than two orders of magnitude during handling the product. Thus, the FEEDAP Panel considers that the additive could pose a health risk upon inhalation.

The nickel content of the additive under assessment was provided and is up to 107 mg/kg. Inhalation of nickel can cause pulmonary toxicity, resulting in bronchitis, fibrosis and lung cancer in humans. The proposed occupational exposure limit (OEL) for the inhalable fraction of water soluble nickel is 0.01 mg Ni/m^3 (European Commission, 2011). The dusting potential of the products

amounted up to 2.7 g/m^3, corresponding to about 0.290 mg Ni/m^3; therefore, the nickel OEL is exceeded by more than one order of magnitude.

The FEEDAP Panel assessed the user exposure resulting from the residual content of chromium in ferric oxide. Using the highest values as a worst-case assumption (dusting potential up to 2.7 g/m^3, chromium content in the additive up to 404 mg/kg, corresponding to 1.09 mg Cr/m^3 dust), the calculated value would be above the threshold limit value set by the ACGIH (2004; 10 μg/m^3 threshold limit value (TLV), time-weighted average (TWA), insoluble Cr(VI) compounds), the action level set by the Occupational Safety & Health Administration (OSHA, 2009; 2.5 μg Cr(VI)/m^3 for an 8-h TWA exposure) and the more recent from the National Institute for Occupational Safety and Health (NIOSH, 2013; recommended exposure limit 0.2 μg Cr(VI)/m^3 for an 8-h TWA exposure, 40-h working week). Considering the magnitude by which these thresholds are exceeded, the FEEDAP concludes that the content of chromium gives rise to a concern for user safety.

The FEEDAP Panel recognises that (i) the use of the TLV or OEL as guidance values for user safety of feed additives may result in overly conservative assessments, as the exposure is unlikely to be so continuous and intense as in an industrial scenario, for which TLVs/OELs have been envisaged, and (ii) no speciation of chromium in ferric oxide was available. Nevertheless, even with the mentioned caveats, a concentration of iron, nickel or chromium in the inhalable dust exceeding the guidance values by at least one order of magnitude points to a risk by inhalation for users.

3.2.4.3. Conclusions on safety for the user

Ferric oxide is irritant to skin and eyes by mechanical action. Owing to the nickel content in the additive, ferric oxide should be considered as dermal and respiratory sensitiser.

Inhalation of ferric oxide, chromium and nickel is a hazard; as exposure by inhalation is likely, handling ferric oxide would be a risk for the users.

As there is concern about the possible genotoxicity of ferric oxide, any route of exposure should be considered as hazardous.

3.2.5. Safety for the environment

Iron oxides are ubiquitous in the environment. Any additional input from the nutritional use in food-producing animals is considered negligible. Moreover, ferric oxide is insoluble in water, and iron from this compound has a very low bioavailability. It is unlikely that the use of ferric oxide in animal nutrition would pose a risk to the environment.

3.3. Efficacy

According to a review of Henry and Miller (1995), ferric oxide has a low bioavailability in different animal species; the authors summarised the relative bioavailability of ferric oxide compared to ferrous sulfate monohydrate (set at 100%) for poultry and pigs as 10% and for sheep and rats as 5%. The NRC (1998) reported a bioavailability of zero. Suttle (2010) stated that ferric oxide is among the poorest sources of inorganic iron and dissuaded from its use in animal feeds. Moreover, ferric oxide is routinely used as an indigestible marker in e.g. digestibility studies (Kerr et al., 2015).

Considering the vital role of iron in haemoglobin synthesis and the need of particularly young animals for immediate keeping the requirements, ferric oxide is not considered an efficacious source of iron. Sporadic findings of a certain and even higher availability are not considered controversial; the use of ferric oxide as iron source would, in case of not providing available iron, severely impair animal health and welfare.

In summary, ferric oxide should not be considered as iron source capable to meet iron requirements of animals.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation[45] and good manufacturing practice.

[45] Regulation (EC) No 183/2005 of the European Parliament and of the Council of 12 January 2005 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

4. Conclusions

The FEEDAP Panel cannot conclude on the safety of ferric oxide for the target animals owing to that (i) the application of ferric oxide red is for all animal species, (ii) lifetime administration to animals is not excluded and (iii) a sufficient biological and toxicological database was not available.

Regarding (i) the very low absorption of iron from the ferric oxide by target animals and (ii) the homoeostatic regulation of iron metabolism in animals, any influence of feeding the ferric oxide on the iron content of edible tissues and products is not expected. The use of ferric oxide in animal nutrition is unlikely to result in a direct exposure of the consumer to this oxide. Consequently, the supplementation of feed for food-producing animals with ferric oxide would likely not constitute a risk to consumers.

Ferric oxide is an irritant to skin and eyes by mechanical action. Owing to the nickel content in the additive, the ferric oxide should be regarded as dermal and respiratory sensitiser. Inhalation of ferric oxide, nickel and chromium is a hazard; since exposure by inhalation is likely, handling ferric oxide would be a risk for the users. As there is concern about the possible genotoxicity of ferric oxide, any route of exposure should be considered as hazardous.

Iron oxides are ubiquitous in the environment. Any additional input from the nutritional use of ferric oxide in food-producing animals is considered negligible. It is unlikely that the use of the additive in animal nutrition would pose a risk to the environment.

Ferric oxide should not be considered as iron source capable to meet iron requirements of animals.

5. Recommendations

The name of the additive under application should be adjusted to the standards established by IUPAC to 'Iron(III) oxide'.

A specification should be set for fluorine and that of mercury should be adjusted to reflect analytical values.

Based on considerations of animal safety, the FEEDAP Panel recommends the modification of some of the currently authorised maximum iron contents in complete feed as follows:

- from 750 to 450 mg Fe/kg for bovine and poultry
- from 1,250 to 600 mg Fe/kg for pets

6. General remark

The FEEDAP Panel is not in a position to derive a maximum safe iron concentration in feed for horses or fish due to insufficient available data. As a provisional measure, the current value for other animal species (750 mg Fe/kg) could be maintained. In the view of the FEEDAP Panel, additional data are required to confirm or modify the current maximum iron content in feed for horses and fish.

Documentation provided to EFSA

1) Dossier Ferric oxide (E1). October 2010. Submitted by Poortershaven Industriële Mineralen B.V.
2) Dossier Ferric oxide (E1). Supplementary information. January 2013. Submitted by Poortershaven Industriële Mineralen B.V.
3) Dossier Ferric oxide (E1). Supplementary information. March 2014. Submitted by Poortershaven Industriële Mineralen B.V.
4) Dossier Ferric oxide (E1). Supplementary information. March 2015. Submitted by Poortershaven Industriële Mineralen B.V.
5) Dossier Ferric oxide (E1). Supplementary information. June 2015. Submitted by Poortershaven Industriële Mineralen B.V.
6) Evaluation report of the European Union Reference Laboratory for Feed Additives on the methods(s) of analysis for Iron (E1).
7) Comments from Member States received through ScienceNet.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ANS Panel	EFSA Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstracts Service
EEC	European Economic Community
EURL	European Union Reference Laboratory
FAO	Food and Agriculture Organization of the United Nations
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
IARC	International Agency for research on Cancer
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MTL	maximum tolerable level
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OSHA	Occupational Safety & Health Administration
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-para-dioxins
TEQ	toxic equivalent factor
TG	Technical Guidance
TLV	threshold limit value
TWA	time-weighted average
WHO	World Health Organization
XRF	X-ray fluorescence

Appendix A – List of Risk Assessment Reports on iron and iron compounds

In addition to the reports cited in the Background section, risk assessments from other the European Union (EU) bodies and Institutions have been carried out.

1) EU risk assessment reports

Food Standard Agency Risk Assessment iron (http://www.food.gov.uk/multimedia/pdfs/evm_iron.pdf). Scientific Advisory Committee on Nutrition Assessment iron (http://www.sacn.gov.uk/pdfs/sacn_iron_and_health_report_web.pdf).

2) EFSA ANS Panel opinions

Iron (II) taurate, magnesium taurate and magnesium acetyl taurate as sources of iron or magnesium added for nutritional purposes in food supplements – Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (http://www.efsa.europa.eu/en/efsajournal/doc/947.pdf).

Ferrous phosphate added for nutritional purposes to food supplements – Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (http://www.efsa.europa.eu/en/efsajournal/doc/951.pdf).

Chromium(III)-, iron(II)- and selenium-humic acid/fulvic acid chelate and supplemented humifulvate added for nutritional purposes to food supplements – Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/en/efsajournal/doc/1147.pdf).

Orotic acid salts as sources of orotic acid and various minerals added for nutritional purposes to food supplements – Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/en/efsajournal/doc/1187.pdf).

Scientific Opinion on the use of ferric sodium EDTA as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses – EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/en/efsajournal/doc/1414.pdf).

Scientific Opinion on the safety of ferrous ammonium phosphate as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses – EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/en/efsajournal/doc/1584.pdf).

Scientific Opinion on the safety of heme iron (blood peptonates) for the proposed uses as a source of iron added for nutritional purposes to foods for the general population, including food supplements – EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/en/efsajournal/doc/1585.pdf).

Scientific Opinion on the re-evaluation of iron oxides and hydroxides (E 172) as food additives – EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4317.pdf).

3) EFSA CEF Panel opinions/EFSA Reports

Scientific Opinion Flavouring Group Evaluation 42: Ion containing organic substances from chemical group 30 (http://www.efsa.europa.eu/en/efsajournal/doc/1191.pdf).

Scientific Report of EFSA on the risk assessment of salts of authorised acids, phenols or alcohols for use in food contact materials (http://www.efsa.europa.eu/en/efsajournal/doc/1364.pdf).

4) EFSA AFC Panel opinions

Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request from the Commission related to a 6th list of substances for food contact materials (http://www.efsa.europa.eu/en/efsajournal/doc/161.pdf).

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Ferrous bisglycinate as a source of iron for use in the manufacturing of foods and in food supplements (http://www.efsa.europa.eu/en/efsajournal/doc/299.pdf).

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to calcium, iron, magnesium, potassium and zinc L-pidolate as sources for calcium, iron, magnesium, potassium and zinc added for nutritional

purposes to food supplements and to foods intended for particular nutritional uses (http://www.efsa.europa.eu/en/efsajournal/doc/495.pdf).

Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) on a request related to a 18th list of substances for food contact materials (http://www.efsa.europa.eu/en/efsajournal/doc/628.pdf).

5) EFSA NDA Panel opinions

Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Iron (http://www.efsa.europa.eu/en/efsajournal/doc/125.pdf).

Lactobacillus plantarum 299v (DSM 9843) and improve iron absorption Scientific substantiation of a health claim related to *Lactobacillus plantarum* 299v (DSM 9843) and improve iron absorption pursuant to Article 13(5) of Regulation (EC) No 1924/2006—Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies (http://www.efsa.europa.eu/en/efsajournal/doc/999.pdf).

Scientific Opinion on the substantiation of health claims related to iron and formation of red blood cells and haemoglobin (ID 249, ID 1589), oxygen transport (ID 250, ID 254, ID 256), energy-yielding metabolism (ID 251, ID 1589), function of the immune system (ID 252, ID 259), cognitive function (ID 253) and cell division (ID 368) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (http://www.efsa.europa.eu/en/efsajournal/doc/1215.pdf).

Scientific Opinion on the substantiation of health claims related to vitamin A and cell differentiation (ID 14), function of the immune system (ID 14), maintenance of skin and mucous membranes (ID 15, 17), maintenance of vision (ID 16), maintenance of bone (ID 13, 17), maintenance of teeth (ID 13, 17), maintenance of hair (ID 17), maintenance of nails (ID 17), metabolism of iron (ID 206), and protection of DNA, proteins and lipids from oxidative damage (ID 209) pursuant to Article 13(1) of Regulation (EC) No 1924/2006—EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1221.pdf).

Scientific Opinion on the substantiation of health claims related to vitamin B6 and protein and glycogen metabolism (ID 65, 70, 71), function of the nervous system (ID 66), red blood cell formation (ID 67, 72, 186), function of the immune system (ID 68), regulation of hormonal activity (ID 69) and mental performance (ID 185) pursuant to Article 13(1) of Regulation (EC) No 1924/2006—EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1225.pdf).

Scientific Opinion on the substantiation of health claims related to vitamin C and protection of DNA, proteins and lipids from oxidative damage (ID 129, 138, 143, 148), antioxidant function of lutein (ID 146), maintenance of vision (ID 141, 142), collagen formation (ID 130, 131, 136, 137, 149), function of the nervous system (ID 133), function of the immune system (ID 134), function of the immune system during and after extreme physical exercise (ID 144), non-haem iron absorption (ID 132, 147), energy-yielding metabolism (ID 135), and relief in case of irritation in the upper respiratory tract (ID 1714, 1715) pursuant to Article 13(1) of Regulation (EC) No 1924/2006—EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1226.pdf).

Scientific Opinion on the Substantiation of a health claim related to Iron and cognitive development of children pursuant to Article 14 of Regulation (EC) No 1924/2006—EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1360.pdf).

Scientific Opinion on the substantiation of health claims related to iron and formation of red blood cells and haemoglobin (ID 374, 2889), oxygen transport (ID 255), contribution to normal energy-yielding metabolism (ID 255), reduction of tiredness and fatigue (ID 255, 374, 2889), biotransformation of xenobiotic substances (ID 258), and 'activity of heart, liver and muscles' (ID 397) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 (http://www.efsa.europa.eu/en/efsajournal/doc/1740.pdf).

Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) and improved bioavailability of nutrients (ID 384, 1728, 1752, 1755), energy and nutrient supply (ID 403, 413, 457, 487, 667, 1675, 1710, 2901, 4496) and presence of a nutrient in the human body (ID 720) pursuant to Article 13(1) of Regulation (EC) No 1924/2006—EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1743.pdf).

Scientific Opinion on the substantiation of health claims related to riboflavin (vitamin B2) and contribution to normal energy-yielding metabolism (ID 29, 35, 36, 42), contribution to normal metabolism of iron (ID 30, 37), maintenance of normal skin and mucous membranes (ID 31, 33), contribution to normal psychological functions (ID 32), maintenance of normal bone (ID 33),

maintenance of normal teeth (ID 33), maintenance of normal hair (ID 33), maintenance of normal nails (ID 33), maintenance of normal vision (ID 39), maintenance of normal red blood cells (ID 40), reduction of tiredness and fatigue (ID 41), protection of DNA, proteins and lipids from oxidative damage (ID 207), and maintenance of the normal function of the nervous system (ID 213) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 – EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/1814.pdf).

Scientific Opinion on the substantiation of health claims related to meat or fish and the improvement of non-haem iron absorption (ID 1223) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 – EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/en/efsajournal/doc/2040.pdf).

Scientific Opinion on the substantiation of a health claim related to iron and maintenance of normal hair growth pursuant to Article 13(5) of Regulation (EC) No 1924/2006 – EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2602.pdf).

Scientific Opinion on bovine lactoferrin – EFSA Panel on Dietetic Products, Nutrition and Allergies (http://www.efsa.europa.eu/en/efsajournal/doc/2701.pdf).

Scientific Opinion on Dietary Reference Values for iron – EFSA Panel on Dietetic Products, Nutrition and Allergies (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4254.pdf).

Appendix B – List of authorisations of iron compounds other than as feed additives

The following iron compounds are authorised for use in food (Regulation (EC) No 1170/2009)[46]: ferrous L-pidolate, ferrous phosphate, iron (II) taurate which may be used in the manufacture of food supplements; ferrous carbonate, ferrous citrate, ferrous ammonium citrate, ferrous gluconate, ferrous fumarate, ferric sodium diphosphate, ferrous lactate, ferrous sulfate, ferric diphosphate (ferric pyrophosphate), ferric saccharate, elemental iron (carbonyl + electrolytic + hydrogen reduced) and ferrous bisglycinate which may be used in the manufacture of food supplements and may be added to food. Ferrous gluconate (579) and ferrous lactate (E 585) are authorised as food additives for use in olives darkened by oxidation at the maximum level of 150 mg/g as Fe (European Parliament and Council Directive No 95/2/EC).[47]

The following iron compounds can be used for the manufacturing of dietetic foods (Commission Regulation (EC) No 953/2009)[48]: ferrous carbonate, ferrous citrate, ferrous ammonium citrate, ferrous gluconate, ferrous fumarate, ferric sodium diphosphate, ferrous lactate, ferrous sulfate, ferric diphosphate (ferric pyrophosphate), ferric saccharate, elemental iron (carbonyl + electrolytic + hydrogen reduced), ferrous bisglycinate and ferrous L-pidolate.

The following iron compounds can be used for the manufacturing of processed cereal-based foods and baby foods for infants and young children (Commission Directive 2006/125/EC)[49]: ferrous citrate, ferrous ammonium citrate, ferrous gluconate, ferrous lactate, ferrous sulfate, ferrous fumarate, ferric diphosphate (ferric pyrophosphate), elemental iron (carbonyl + electrolytic + hydrogen reduced), ferric saccharate, sodium ferric diphosphate and ferrous carbonate.

Regarding pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin, the following iron compounds are listed in table 1 of the Annex of Regulation 37/2010[50] as *Allowed substances, no MRL required*: iron ammonium citrate, iron dextran, iron dichloride, iron fumarate, iron glucoheptonate and iron sulfate.

The following iron compounds are listed in Annex of Commission Implementing Regulation (EU) 40/2011[51] as 'Active substances approved for use in plant protection products': iron sulfate, iron (II) sulfate anhydrous, iron (II) sulfate monohydrate, iron (II) sulfate heptahydrate (iron (II) sulfate) and ferric phosphate.

The following type of fertilisers for iron are listed in Annex I of Regulation (EC) No 2003/2003 of the European Parliament and of the Council as *Fertilisers containing only one micro-nutrient*[52]: (a) iron salt (chemically obtained product containing a mineral iron salt as its essential ingredient); (b) iron chelate (water soluble product obtained by chemical reaction of iron with chelating agents mentioned in the list of Annex I chapter E.3 which are sodium, potassium or ammonium acids or salts of EDTA, DTPA, EDDHA, HEEDTA, EDDHMA, EDDCHA) and iron fertiliser solution (product obtained by dissolving types (a) and/or one of the type (b) in water).

The following iron compounds can be used for cosmetic purposes (Regulation (EC) No 1223/2009 of the European Parliament and of the Council[53]): iron oxide, iron oxide red, iron oxide yellow, iron oxide black, ferric ammonium ferrocyanide, aluminium silicate coloured with ferric oxide and natural hydrated aluminium silicate, $Al_2O_3 \cdot 2SiO_2 \cdot 2H_2O$ with iron carbonates or ferric hydroxide impurities.

[46] Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p. 36.

[47] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners. OJ L 61, 18.3.1995, p. 1.

[48] Commission Regulation (EC) No 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses. OJ L 269, 14.10.2009, p. 9.

[49] Commission Directive 2006/125/EC of 5 December 2006 on processed cereal-based foods and baby foods for infants and young children. OJ L 339, 6.12.2006, p. 16.

[50] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. OJ L 15, 20.1.2010, p. 1.

[51] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1.

[52] Regulation (EC) No 2003/2003 of the European Parliament and of the Council of 13 October 2003 relating to fertilisers. OJ L 304, 21.11.2003, p. 1.

[53] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. OJ L 342, 22.12.2009, p. 59.

According to the Annex of Regulation (EC) No 432/2012[54], the following health claims can be made only for food which is at least a source of iron as referred to in the claim SOURCE OF [NAME OF VITAMIN/S] AND/OR [NAME OF MINERAL/S] as listed in the Annex to Regulation (EC) No 1924/2006[55]: iron contributes to normal cognitive function, iron contributes to normal energy-yielding metabolism, iron contributes to normal formation of red blood cells and haemoglobin, iron contributes to normal oxygen transport in the body, iron contributes to the normal function of the immune system, iron contributes to the reduction of tiredness and fatigue and iron has a role in the process of cell division.

[54] Commission Regulation (EC) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health. OJ L 136, 25.5.2012, p. 1.
[55] Regulation (EC) No 1924/2006 of the European Parliament and of the council of 20 December 2006 on nutrition and health claims made for food. OJ L 404, 30.12.2006, p. 9.

Appendix C – Iron content in animal tissues and products: food composition tables

Table C.1: Iron content of animal tissues (liver, kidney and muscle) and products (egg and milk): data derived from food composition tables

Species/ category	Liver (mg Fe/kg)	Kidney (mg Fe/kg)	Muscle (mg Fe/kg)	Egg (mg Fe/kg)	Milk (mg Fe/kg)	Reference
Swine						
Pigs		33	5.5–7.1			(c)
	180[(a)]		12–17			(d)
	170 (150–310)	73 (53–150)	10 (10–11)			(e)
Ruminants						
Veal		60.8	14.5–16			(c)
			12			(d)
	55 (57–93)	120 (79–150)	21 (15–26)			(e)
Cattle			16–24.7			(c)
	88	80	13–19			(d)
	69 (44–72)	110 (65–150)	21 (17–23)			(e)
Dairy cattle					0.6	(c)
					1	(d)
					0.46 (0.3–0.7)	(e)
Lamb			12–22			(c)
			17–20			(d)
Sheep	126				1	(e)
	120 (120–130)	75 (41–92)	18 (15–23)		0.58 (0.51–1.0)	(c)
Goat					1	(d)
					0.41 (0.36–0.75)	(e)
Poultry						
Chickens	90.15		18			(c)
			6–14			(d)
	74		7.3 (6–20)			(e)
Laying hens	70.6		8–10.1	20 55 [yolk]		(c)
				15		(d)
				18		(e)
				72 (51–120) [yolk]		
Hens			16			(d)
Turkey			7.7			(c)
			9–10			(d)
Duck	300.5		12	38.5		(c)
			13			(d)
Goose			25	36.4		(c)
	290.6		18			(d)
Rabbits			10			(d)
			27 (18–60)			(e)
Horses			35			(c)
	90		39			(d)
			49			(e)

Species/ category	Liver (mg Fe/kg)	Kidney (mg Fe/kg)	Muscle (mg Fe/kg)	Egg (mg Fe/kg)	Milk (mg Fe/kg)	Reference
Fish						
Cod			23			(d)
Herring			13			(c)
			9			(d)
			9.8 (5.9–10)			(e)
Mackerel			12			(d)
			12 (8–14)			(e)
Eel			10			(d)
Trout			7			(c)
			20[(b)]			(d)
			4.1			(e)
Tuna			15			(c)
			13			(d)
Carp			10			(d)
			7 (6–13)			(e)
Salmon			8			(c)
			7			(d)
			5.8 (4–15)			(e)

(a): Data are reported as from the reference, i.e. as a single figure, as average (and range) or as a range.
(b): Farmed trout.
(c): Danish Food Consumption Databank – Ed. 7.01. National Food Institute – Technical University of Denmark. http://www.foodcomp.dk/v7/fcdb_foodnutrlist.asp?CompId=0061
(d): Database of INRAN – Italian National Institute for Research on Foods and Nutrition. http://www.inran.it/646/tabelle_di_composizione_degli_alimenti.html
(e): Souci SW, Fachmann W and Kraut H, 2008. Food composition and nutrition tables. 7th Edition, MedPharm Scientific Publisher, Stuttgart, Germany; and CRC Press, Taylor and Francis Group, LLC, Boca Raton, Florida, USA.

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Iron (E1)

In the current application authorisation is sought under articles 4(1) and 10(2) for ferrous chelate of glycine hydrate,[1] ferrous/iron chelate of amino acids hydrate,[1,2] ferrous fumarate,[1] ferric oxide,[3] ferric chloride hexahydrate,[1] ferrous sulfate monohydrate,[1,4] ferrous sulfate heptahydrate,[1,5] ferrous carbonate[6] under the category/functional group (3b) 'nutritional additives'/'compounds of trace elements', according to the classification system of Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought for the use of these feed additives for all categories and species.

According to the Applicants *ferrous chelate of glycine hydrate* is a green-gray free-flowing powder with a minimum content of 17% *total iron*, *ferrous/iron chelate of amino acids hydrate* is a brown free-flowing powder with a minimum content of 10% *total iron*, *ferrous fumarate* is white reddish powder with a minimum content of 30% *total iron*, *ferric oxide* is a red brown powder with a minimum content of 56% *total iron*, *ferric chloride hexahydrate* is a yellow brown solid aggregate with a minimum content of 59% *total iron*, *ferrous sulfate monohydrate* consists of beige to gray free-flowing granules with a minimum content of 29% *total iron*, *ferrous sulfate heptahydrate* is a blue-green crystalline powder with a minimum content of 18% *total iron* and *ferrous carbonate* is a brown powder with a minimum content of 37% *total iron*. These *feed additives* are intended to be mixed into premixtures, feedingstuffs and/or water(*). The Applicants suggested maximum levels ranging from 250 to 1,250 mg *total iron*/kg *feedingstuffs* and from 100 to 2,273 mg *total iron*/L *water*, similar to limits set in the previous regulations.

For the identification and quantification of the inorganic iron compounds (i.e. *ferrous fumarate*, *ferric chloride hexahydrate* and *ferrous sulphate mono and heptahydrate*) in the feed additive, the EURL recommends for official control the relevant titrimetric methods described in the European Pharmacopoeia Monographs 0083, 0902 and 1515. As for the identification of *ferrous carbonate* and *ferric oxide* the EURL recommends using X-ray diffraction.

For the determination of *ferric oxide* (also known as iron oxide red) in the feed additive the internationally recognised FAO JECFA monograph for food additives is recommended by Commission Directive 2008/128/EC, laying down specific purity criteria concerning colours for use in foodstuffs. Identification is based on solubility in solvents, while quantification is based on digestion and iodometric titration.

For the quantification of 'amino' content in the amino iron chelates (i.e. *ferrous chelate of glycine hydrate* and *ferrous/iron chelate amino acids hydrate*), the Applicant proposed the Community method based on ion exchange chromatography combined with post-column ninhydrin derivatisation and photometric detection at 570 nm. The EURL considers the Community method suitable for the characterisation of the amino compounds in the frame of official control.

Furthermore, the EURL identified the generic European Pharmacopoeia methods for the 'identification reactions of ions and functional groups', such as carbonate, chloride and sulfate in the *feed additives*. Finally, the EURL recommends crystallographic techniques, such as X-Ray diffraction for the characterisation of crystalline structures of *ferric oxide*, *ferric chloride hexahydrate, ferrous carbonate* and *ferrous sulfate mono* and *heptahydrate*.

For the quantification of total iron in the *feed additives*, *premixtures* and *feedingstuffs* the Applicants submitted three ring trial validated CEN methods: EN 6869, based on atomic absorption spectrometry (AAS), EN 15510, based on inductively coupled plasma atomic emission spectroscopy (ICP-AES) and CEN/TS 15621, based on ICP-AES after pressure digestion. Precisions ranging from 2% to 16% were reported, together with limits of quantification (LOQ) ranging from 1 to 5 mg/kg *feedingstuffs*. Furthermore, the EURL identified the comparative trial organised by the UK Food Standards Agency, based on the Community method for the determination of iron in *feedingstuffs*, in which precisions ranging from 1.0% to 9.5% were reported.

For the quantification of total iron in *water* the Applicant (FAD-2010-0095) submitted the ring trial validated method EN ISO 11885, based on ICP-AES. The following performance characteristics were

[1] FAD-2010-0095.
[2] FAD-2010-0068.
[3] FAD-2010-0236.
[4] FAD-2010-0295.
[5] FAD-2010-0296.
[6] FAD-2010-0380.

reported: a relative standard deviation for *repeatability* (RSDr) ranging from 1.5% to 2.4%, a relative standard deviation for *reproducibility* (RSDR) ranging from 4.9% to 5.9%, and LOQ = 1 μg/L.

Based on the available performance characteristics the EURL recommends for official control all the above mentioned CEN methods together with the Community method to quantify total iron content in the *feed additives*, *premixtures*, *feedingstuffs* and/or *water*.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.

(*) not for ferric oxide, ferrous carbonate and ferrous chelate of amino acids hydrate.