SCIENTIFIC OPINION

Inability to assess the safety of iron-enriched yeast as a source of iron, added for nutritional purposes to foods for particular nutritional uses and foods (including food supplements) intended for the general population, based on the supporting dossiers [1]

Scientific Statement of the Panel on Food Additives and Nutrient Sources added to Food (ANS)

(Question No EFSA-Q-2005-095, EFSA-Q-2005-206, EFSA-Q-2006-214)

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PANEL MEMBERS

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[1] For citation purposes: Scientific Statement of the Panel on Food Additives and Nutrient Sources added to Food on the inability to assess the safety of iron-enriched as a source of iron, added for nutritional purposes to foods for particular nutritional uses and foods (including food supplements) intended for the general population, based on the supporting dossiers following a request from the European Commission. *The EFSA Journal* (2009) 1130, 1-8.

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The European Community legislation lists nutritional substances that may be used for nutritional purposes in certain categories of foods as sources of certain nutrients.

The Commission has received a request for the evaluation of iron-enriched yeast added for nutritional purposes to foodstuffs. The relevant Community legislative measure is:

- Commission Directive 2001/15/EC on substances that may be added for specific nutritional purposes in food for particular nutritional uses[2]
- Directive 2002/46/EC of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements[3].
- Regulation (EC) 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods[4]

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, based on its consideration of the safety and bioavailability of iron-enriched yeast added for nutritional purposes in foods for particular nutritional uses and foods (including food supplements) intended for the general population.

[2] OJ N° L 52, 22.2.2001, p. 19.
[3] OJ N° L 183, 12.7.2002, p.51.
[4] OJ N° L 404, 30.12.2006, p 26.

STATEMENT

1. Introduction

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to provide a scientific opinion on the safety of iron-enriched yeast as a source of iron, added for nutritional purposes to foods for particular nutritional uses and foods (including food supplements) intended for the general population, and on the bioavailability of iron from this source.

This statement is based on the information on iron-enriched yeasts provided by three petitioners.

2. Summary of the information provided in the supporting dossiers on iron-enriched yeasts

Iron-enriched yeasts are derived from cultures of specified strains of *Saccharomyces cerevisiae* grown in the presence of ferrous sulphate or ferrous fumarate. Fermentation takes place at a specified temperature and pressure for defined periods of time. This is followed by increasing the temperature to kill the yeast. The cell wall is ruptured to release the contents which are then spray dried.

According to one of the petitioners, iron in iron-enriched yeast is naturally integrated by the growing yeast into its own structure and occurs therefore, in the way iron would be present in any food material. Another petitioner describes iron-enriched yeast as “a complex of proteins, peptides and amino acids, resulting from the hydrolysis of *Saccharomyces cerevisiae*, which are bound to iron”.

One of the petitioners states that during fermentation in the presence of ferrous fumarate, a specific strain of *Saccharomyces cerevisiae* produces specific iron compounds, the metabolic fate and the biological distribution of which are similar to those of other sources of iron in the diet.

No specific chemical identity (name, CAS Registry Number, molecular weight) was provided by any of the petitioners and the petitioners named their products differently. One of the petitioners states that “the integration will be chemically multi-formatted by the organism and therefore, its chemical name, formula, chemical family and CAS Registry Number is undefined”.

The analytical techniques which have been used to characterise the formation of a bound iron-yeast complex are Fourier Transform Infrared (FTIR) Spectroscopy and a comparative elemental analysis for carbon, hydrogen, and nitrogen (C:H:N analysis).

Chemical and microbiological specifications have been provided by the three petitioners. Iron-enriched yeasts are described as an off white powder or an amorphous hygroscopic brown powder, soluble in water, hazy at 5%; in one case the range of pH was given (4.5-5.8). The total content of iron in the products from the different petitioners is in the range of 5.0 to 5.7%, the remainder of the material is made up of ruptured yeast cells

The manufacturing process was described in detail by one petitioner. The other petitioners provided brief details of the manufacturing process.

Iron-enriched yeasts are stated by two petitioners to be used as an ingredient in tablets, caplets, capsules, chewable tablets, effervescent powders and liquids. that are food supplements. Iron-enriched yeast was identified by one applicant as currently used in four products where the iron content varies between 2-20 mg/day and another petitioner indicated that these supplements containing iron-enriched yeast are intended to provide in the range of 1-7 mg iron/day. Specific proposals for use levels for iron-enriched yeast were not provided by the third petitioner.

Two petitioners stated that iron from iron-enriched yeasts is more bioavailable than ferrous fumarate and is better tolerated. Some studies comparing the absorption of iron enriched yeasts with other sources of iron were provided (Vinson and Bose, 1981; Vinson *et al.,* 1989; Korniewicz *et al.,* 2007; Dobrzański *et al.*, 2008a,b). A description of the specifications of the iron-enriched yeast used in the studies of Vinson *et al.* has been provided by one of the petitioners.

In the Vinson and Bose (1981) study, the bioavailability of various forms of iron has been investigated in studies in rats. Three groups of five rats each were fed a commercial iron-deficient diet for 2 to 4 weeks to produce a state of iron deficiency.

Each group was then fed supplemental iron in one of three forms: an inorganic iron salt (iron sulphate), iron amino acid chelate and iron-enriched yeast. After this period of supplementation, the rats were sacrificed and the concentration of iron was determined in the blood and liver. The slope of the plot of iron concentration in the diet *vs.* iron concentration in the blood or liver indicated that iron was bioavailable from all three sources. The authors concluded that the results showed that iron from iron-enriched yeast was the most bioavailable form of iron, but that iron-enriched yeast and iron sulphate were very similar in their blood bioavailability.

In the study of Korniewicz *et al.* (2007), relative absorption and excretion of dietary iron was measured in piglets (5 per group) given a control diet or one containing iron-enriched yeast (*Saccharomyces cerevisiae* yeasts containing 32.0 g iron in 1 kg of dry product) (Korniewicz *et al.,* 2007). Both the control diet and the yeast-enriched diet contained 178 mg iron/kg diet (equivalent to approximately 6 mg/kg bw/day) of which 27% was supplemented in the form of either iron-enriched yeast or, in the case of the control diet, ferric sulphate. The amount of iron absorbed and excreted was calculated by comparing faecal and urinary iron excretion every four days during a 3-week feeding period with the respective diets. The amount of iron excreted in the faeces by the two groups of animals was similar, at approximately 25%, and absorption of iron was 73% in the control group and 74.9% in the group given iron-enriched yeast. There were however differences between the urinary excretion of iron in the two groups, approximately 6% of the total iron intake of the control group was excreted in urine, while for the group supplemented with iron-enriched yeast this figure was 17%. The authors attributed this to the higher solubility of the iron from iron-enriched yeast. The net result of the increased excretion of iron from iron-enriched yeast was that retention of the total amount of consumed iron was significantly lower ($p<0.05$) in this experimental group (58%) than in the control group (67.4%). The authors concluded that in feeding pigs, yeast enriched with iron, was found to be less efficient as a source of iron than the inorganic iron salt (iron sulphate).

In the Dobrzanski *et al.* (2008a) study, standard feed mixture for 12 laying hens was supplemented with dried *Saccharomyces cerevisiae* yeast enriched with iron. The availability of iron (described as “organic forms”) from the iron-enriched yeast compared to the inorganic form iron sulphate ($FeSO_4$) given to another group of hens was assessed by analysis of the iron content in the diet, droppings and eggs. However, the differences in iron availability from inorganic and organic sources were not statistically confirmed. In a following paper, the same authors assessed the bioaccumulation of iron in eggs, whole blood and feathers of hens (Dobrzanski *et al.*, 2008b). Introduction of organic forms of iron to feed did not cause any significant changes in the iron content in eggs, blood and feathers of hens compared to the control group.

No toxicological data were provided on iron-enriched yeasts.

3. Assessment

The Panel notes that *Saccharomyces cerevisiae* has a qualified presumption of safety (EFSA, 2008) but considers that this presumption of safety might not be applicable to the specific conditions of culture of the yeasts in the presence of a high quantity of iron.

According to one of the petitioners, fermentation in the presence of iron within eukaryotic cells will produce iron compounds not otherwise defined but with a metabolic fate and biological distribution similar to those of other food sources of iron in the diet.

According to the same petitioner, the difference in the C:H:N ratio between the starter yeast and the iron-enriched yeast supports the hypothesis that changes within the yeast due to the incorporation of iron into the internal structure of the yeast may have modified the overall composition of the yeast. However the Panel considers that the C:H:N analysis is not relevant to compare the starter yeast and the iron-enriched yeast and that such a difference in the C:H:N ratio would not in any case provide a clear evidence of incorporation of iron or change in the structure of the yeast.

According to the petitioners, the differences between the FTIR spectra of iron-enriched yeast and the starter yeast reference spectrum suggest changes in composition and structure within the yeast. The Panel considers that the FTIR spectra provided do not demonstrate the existence of coordinate bonds between iron and the yeast biomass.

According to the petitioners iron-enriched yeast is safe. Although not explicitly stated in the dossier the argument for the safety of iron-enriched yeast appears to be based on iron being a normal constituent of the diet, and the long history of use of *Saccharomyces cerevisiae* in fermented food and beverages. The assumption is that provided there is no overload of normal metabolic pathways, fermentation within eukaryotic cells will produce iron compounds with a similar metabolic fate and biological distribution similar to those of other sources of iron in the diet.

The Panel considers that the petitioners have insufficiently chemically characterised their products and therefore have not demonstrated that iron from iron-enriched yeast has a similar metabolic fate and biological distribution similar to those of other sources of iron in the diet.

The petitioners stated that iron from iron-enriched yeasts is more bioavailable than iron from inorganic iron compounds. Information supporting this was provided by one petitioner, based on a study carried out in rats (Vinson and Bose, 1981). However this is not fully confirmed by a study in pigs (Korniewicz *et al.*, 2007) which concluded that iron-enriched yeast was less efficient as a source of iron than ferric sulphate. Although both forms were absorbed to a similar extent, a higher amount of the iron absorbed from iron-enriched yeast was excreted in urine, leading to a lower retention of the iron given in this form than iron from ferric sulphate. Higher bioavailability was also not confirmed in another study in hens (Dobrzanski *et al.*, 2008b), where the authors have shown that introduction of iron-enriched yeast to feed did not cause any significant changes in the iron content in eggs, blood and feathers.

Based on the information provided by one petitioner, the Panel notes that the iron-enriched yeast used in the Vinson studies (Vinson and Bose, 1981, Vinson *et al*., 1989) appears to be similar to one of the iron-enriched yeasts under consideration in this statement. The Panel therefore concludes that iron could be expected to be bioavailable from this iron-enriched yeast. Another petitioner claims that the iron-enriched yeast used in the study by Vinson and Bose (l981) is manufactured in the same way as their product. However, in the absence of further relevant information, the Panel is unable to extrapolate this conclusion on bioavailability to the iron-enriched yeast produced by this petitioner. The Panel is also unable to extrapolate this conclusion to the third iron-enriched yeast under consideration for which no similar information on bioavailability of iron from iron-enriched yeast was provided.

The Panel notes that neither safety data nor suitable supporting references were provided to support the assumption of safety of the iron-enriched yeasts under consideration.

CONCLUSIONS

The Panel concludes that iron could be expected to be bioavailable from one of the iron-enriched yeasts under consideration. The Panel concluded that the bioavailability of the other two iron-enriched yeasts cannot be assessed due to the lack of appropriate dossiers.

The Panel also concludes that due to the lack of appropriate dossiers supporting the use of iron-enriched yeasts in foods for particular nutritional uses and foods (including food supplements) intended for the general population, the safety of iron-enriched yeasts under consideration cannot be assessed.

Key words:

Food supplements, iron, ferrous sulphate, ferrous fumarate, yeast-transformed iron, iron-enriched yeast.

DOCUMENTATION PROVIDED TO EFSA

1. Technical dossier 2005a. Dossier on iron-enriched yeast (iron-enriched *Saccharomyces cerevisiae*) proposed for addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. March 2005. Submitted by Nature’s Own Limited, UK.
2. Technical dossier 2005b. Dossier on Bio-transformed iron proposed for addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. Original submission June 2005; Additional information submitted January 2008 and November 2008. Submitted by Higher Nature Ltd, UK.
3. Technical dossier 2005c. Dossier on yeast enriched with iron. August 2005. Submitted by Vireco Producing Developing Trading and Services Co. Ltd, Hungary.

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GLOSSARY / ABBREVIATIONS

ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS)
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
FTIR	Fourier Transform Infra Red