European Food Safety Authority

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SCIENTIFIC OPINION

Iron (II) taurate, magnesium taurate and magnesium acetyl taurate as sources of iron or magnesium added for nutritional purposes in food supplements [1]

Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food

(Questions No EFSA-Q-2005-217, EFSA-Q-2005-178, EFSA-Q-2006-187, EFSA-Q-2006-288)

Adopted on 29 January 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority, 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 (II) taurate, magnesium taurate and magnesium acetyl taurate added for nutritional purposes as sources of iron or magnesium in food supplements and on the bioavailability of iron or magnesium from these sources.

The present opinion deals only with the safety of iron (II) taurate, magnesium taurate and magnesium acetyl taurate to be used in food supplements intended for the general population, and the bioavailability of iron or magnesium from these sources. The safety of iron and magnesium, in terms of amounts that may be consumed, is outside the remit of this Panel.

The Scientific Committee on Food (SCF) in 2001 as well as the Expert Group on Vitamins and Minerals (EVM) in 2003 concluded that there are insufficient data to establish a safe upper level for iron.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on iron (II) taurate, magnesium taurate and magnesium acetyl taurate as sources for iron or magnesium to be added as a nutritional substance in food supplements following a request from the European Commission. *The EFSA Journal* (2009) 947, 1-30.

For guidance purposes, the EVM established a supplemental intake of iron of approximately 17 mg/day (equivalent to 0.28 mg/kg bw/day for a 60 kg adult) that would not be expected to produce adverse effects in the majority of people.

The petitioner indicated that the quantity of iron (II) taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 14 mg iron/day. This amount is below the guidance value for supplemental intake proposed by the EVM in 2003. A dose of 14 mg iron from iron (II) taurate is equivalent to 76 mg iron (II) taurate, providing 62 mg taurate.

The petitioner indicated that it is possible that the taurine used in the manufacturing process may be produced using genetically modified micro-organisms but the Panel concludes that these sources are not part of the present opinion because they would require a separate submission under Regulation (EC) No 1829/2003.

For magnesium, the SCF has established a Tolerable Upper Intake Level (UL) of 250 mg magnesium per day for supplement use.

The petitioner for magnesium taurate indicated that the quantity of magnesium taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 250 mg magnesium/day which equals the SCF's UL. The amount of 250 mg magnesium is provided by 2804 mg magnesium taurate providing 2554 mg taurate.

The petitioner for magnesium acetyl taurate indicated that use levels of magnesium acetyl taurate in food supplements may amount to a dose of 250 to be taken 1 to 3 times a day. This amounts to 250 to 750 mg magnesium acetyl taurate/day providing 17 to 51 mg magnesium/day and 233 to 699 mg acetyl taurate/day.

Iron (II) taurate and magnesium taurate

Iron (II) taurate and magnesium taurate are readily soluble in water, and therefore the Panel concludes that the bioavailability of iron and magnesium from these sources is expected to be similar to that of other dissociable sources of iron and magnesium in the diet.

The exposure to taurate resulting from the proposed use and use levels of iron (II) taurate and magnesium taurate would amount to 62 + 2554 mg, respectively = 2616 mg taurate/day, which would amount to 43.6 mg taurate/kg bw/day for a 60 kg person.

In 1999 and in 2003 the SCF expressed opinions on caffeine, taurine (taurate) and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks. The SCF 1999 opinion stated that normal dietary intake of taurine is between 40 mg and 400 mg/day which amounts to 0.7 to 6.7 mg/kg bw/day for a 60 kg person. Exposure to 2616 mg taurate/day would be significantly higher than this normal dietary intake. The SCF also concluded that toxicological studies did not reveal any indication of a genotoxic, teratogenic or carcinogenic potential of taurine.

In 2003 the SCF evaluated a 13-week rat study with taurine at dose levels of 0, 300, 600 and 1000 mg/kg bw/day, which showed no significant changes in pathological parameters, but did show the occurrence of significant behavioural effects (increased activity and self-chewing), and possibly impaired motor performance, which could have been mediated via a pharmacological action on the central nervous system. In view of this, the SCF was of the opinion that focused neurological studies were needed and that the absence of a no-observed-adverse-effect-level (NOAEL) for these effects precluded the setting of a safe upper level for daily exposure to taurine.

In 2009 the ANS Panel of EFSA expressed an opinion on taurine and D-glucurono-γ-lactone in "energy" drinks. The ANS Panel evaluated a new 13-week oral toxicity and neurotoxicity study in male and female rats, which included functional observational battery and locomotor activity tests. The new study confirmed the NOAEL of 1000 mg/kg bw/day (the highest dose level tested) established in the earlier 13-week study already described by the SCF in 2003, and provided evidence for a NOAEL of 1500 mg/kg bw/day for behavioural effects. The ANS Panel considered the results of this study to be sufficient to address the previously raised concerns, notably the observation on increased activity and possible decrements in motor skills on the rotarod.

This NOAEL of at least 1000 mg/kg bw/day is 23-fold higher than the estimated combined exposure to taurate from use levels proposed by the petitioner for iron (II) taurate and magnesium taurate.

Given the facts that the NOAEL was the highest dose tested and that taurate is a natural body constituent, the Panel concludes that this margin of safety is sufficient. The Panel recognises that the major exposure to taurate (2554 mg) would come from the use of magnesium taurate as a source of magnesium as compared to an exposure of only 62 mg taurate resulting from the proposed use levels for iron (II) taurate.

The margin of safety for the daily exposure to 62 mg taurate (amounting to 1 mg/kg bw/day for a 60 kg person) resulting from the proposed use levels of iron (II) taurate would be almost 1000 and based on this margin of safety the Panel concludes that the use of iron (II) taurate as a source of iron is not of safety concern.

The margin of safety for the intake of 2554 mg taurate (amounting to 42.6 mg/kg bw/day for a 60 kg person) resulting from the proposed use of magnesium taurate up to dose levels of 250 mg magnesium a day would be 23. Given the facts that the NOAEL was the highest dose tested and that taurate is a natural body constituent, the Panel concludes that this margin of safety is sufficient and that the use of magnesium taurate as a source of magnesium at the proposed use levels is not of safety concern.

The Panel notes that in addition to the diet and the supplement sources evaluated in this Opinion "energy" drinks can also be an important source of taurine (taurate). Combined intake of taurine from magnesium taurate and iron taurate from supplements at the proposed use levels, from "energy" drinks at the mean intake of 8.3 mg/kg bw/day and from the diet at 0.7 to 6.7 mg/kg bw/day would result in an exposure of 52.6 to 58.9 mg taurate/kg bw/day for a 60 kg person, resulting in a margin of safety of 17 to 19. Given the facts that the NOAEL was the highest dose level tested and that taurine is a natural body constituent, the Panel concludes that this margin of safety is sufficient.

Magnesium acetyl taurate

Magnesium acetyl taurate is readily soluble in water and therefore the Panel concludes that the bioavailability of magnesium from these sources is expected to be similar to that of other dissociable sources of magnesium in the diet.

Use of magnesium acetyl taurate at the proposed use levels would result in exposure to 233 to 699 mg acetyl taurate/day equal to 3.88 to 11.65 mg acetyl taurate/kg bw/day, and 17 to 51 mg magnesium/day for a 60 kg person.

The Panel notes that the proposed use levels of magnesium acetyl taurate result in exposure to magnesium at a level below the SCF's UL of 250 mg magnesium per day for supplement use.

The Panel notes that the toxicological database on acetyl taurine is limited. A 3-month oral toxicity study in rats revealed a NOAEL of 2250 mg/kg bw/day. Comparison of this NOAEL to the intake of acetyl taurate that would result from the proposed use levels of magnesium acetyl taurate of 3.9 to 11.7 mg acetyl taurate/kg bw/day results in a margin of safety of 192 to 577. Given the facts that the compound is an acetylated form of taurine and may thus represent a normal endogenous metabolite of taurine and that the compound does not contain a structural alert for genotoxicity the Panel considers this margin of safety adequate and concludes that the use of magnesium acetyl taurate as a source for magnesium at the proposed levels of use is not of safety concern.

The Panel concludes that the bioavailability or iron and magnesium from iron (II) taurate, magnesium taurate and magnesium acetyl taurate is expected to be similar to that of other dissociable sources of iron and magnesium in the diet.

The Panel concludes that the use of iron (II) taurate, magnesium taurate and magnesium acetyl taurate as sources of iron and magnesium at the proposed use levels is not of safety concern.

Key words:

Food supplements, iron (II) taurate, magnesium taurate, magnesium acetyl taurate, CAS Registry Number 75350-40-2.

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BACKGROUND AS PROVIDED BY THE 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 (II) taurate, magnesium taurate and magnesium acetyl taurinate added for nutritional purposes to food supplements. The relevant Community legislative measure is:

- 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[2].

TERMS OF REFERENCE AS PROVIDED BY THE 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 (II) taurate, magnesium taurate (taurinate) and magnesium acetyl taurinate (synonym for magnesium acetyl taurate) added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of Working Group B on Food Additives and Nutrient Sources for the preparation of this opinion: D. Boskou, R. Charrondiere, B. Dusemund, D. Gott, T. Hallas-Møller, K.F.A.M. Hulshof, J. König, D. Parent-Massin, I.M.C.M. Rietjens, G.J.A. Speijers, P. Tobback, T. Verguieva, R.A. Woutersen.

[2] OJ L 183, 12.7.2002, p.51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety and bioavailability of particular sources of iron (II) and magnesium to be used in food supplements intended for the general population. The safety of iron and magnesium, in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Taurine (beta-amino ethane sulphonic acid) is also called taurate when in its deprotonated form and is a naturally occurring beta-amino acid.

Iron (II) taurate

Iron (II) taurate is a pale green powder that is soluble in water. Synonyms for iron (II) taurate are iron (II) taurinate, iron (II) 2-aminoethane sulfonic acid, iron (II) ditaurate and ferrous taurate. A CAS Registry Number for iron (II) taurate is not available. The molecular formula of iron (II) taurate is $Fe(C_2H_6NS0_3)_2$ and the molecular weight of the anhydrous form is 304.11 g/mol. The structural formula is given in Figure 1:

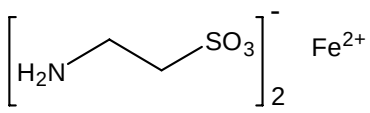

Figure 1. **Structural formula for iron (II) taurate**

Magnesium taurate

Magnesium taurate is a white to off-white powder that is soluble in water. Synonyms for magnesium taurate are: magnesium taurinate, magnesium 2-aminoethane sulfonic acid and magnesium ditaurate. A CAS Registry Number for magnesium taurate is not available. The molecular formula is $C_4H_{12}N_2O_6S_2Mg$ and the molecular weight of the anhydrous form is 272.58 g/mol. The structural formula of magnesium taurate is presented in Figure 2.

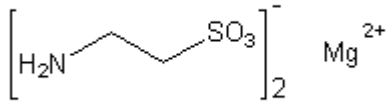

Figure 2. **Structural formula for magnesium taurate**

Magnesium acetyl taurate

Magnesium acetyl taurate is a white powder that is soluble in water. Synonyms for magnesium acetyl taurate are: magnesium acetyl taurinate, ATA-Mg, magnesium acetyl taurinate dehydrate and magnesium 2- acetylamino ethane sulfonic acid. The CAS Registry Number for magnesium acetyl taurate is 75350-40-2. The molecular formula of magnesium acetyl taurate is $C_8H_{16}MgN_2O_8S_2$ and the molecular mass of the anhydrous form is 356.65 g/mol. The structural formula is given in Figure 3.

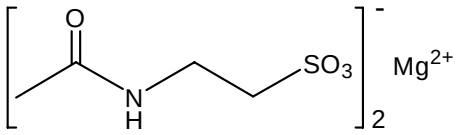

Figure 3. **Structural formula for magnesium acetyl taurate**

The petitioner indicated that the N-acetylation of the amine moiety of taurate in magnesium acetyl taurate modifies the polarity of the taurate molecule, making it more lipophilic enabling easier membrane passage (Bidri and Choay, 2003).

2.2. Specifications

Iron (II) taurate

The petitioner indicated that the purity of iron (II) taurate is at least 98.0 %. The following limits for impurities were defined by the petitioner: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg. Loss on drying is not more than 5 %.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of heavy metals lead, mercury and cadmium, in food supplements as sold should be 3.0 mg/kg, 0.1 mg/kg and 1.0 mg/kg, respectively.

On a molecular weight basis the percentage of iron in iron (II) taurate amounts to 8.9 %.

Magnesium taurate

One petitioner indicated that the purity of magnesium taurate is at least 98.0 % for the anhydrous form. Limits for impurities specified by this petitioner are as follows; mercury lower than 1 mg/kg, arsenic lower than 3 mg/kg, and lead lower than 5 mg/kg.

The other petitioner indicated that the magnesium content is 8.11% (7.7-8.52 %) (ICP-OES) and indicates limits for heavy metals as follows: cadmium < 5 mg/kg, arsenic < 3 mg/kg, and lead < 10 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of heavy metals lead, mercury and cadmium, in food supplements as sold should be 3.0 mg/kg, 0.1 mg/kg and 1.0 mg/kg, respectively.

On a molecular weight basis the percentage of magnesium in magnesium taurate amounts to 18.4 %.

Magnesium acetyl taurate

The petitioner indicated that magnesium acetyl taurate contains 6.5 to 6.9 % magnesium and 91.0 to 95.5 % acetyl taurate. Theoretical values would amount to 6.8 % magnesium and 93.2 % acetyl taurate. Impurities are: taurate not higher than 2%, organic solvents (ethyl acetate and ethanol) not more than 5000 mg/kg, acetic acid not more than 0.1%, heavy metals less than 20 mg/kg and arsenic less than 2 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of heavy metals, lead, mercury and cadmium, in food supplements as sold should be 3.0 mg/kg, 0.1 mg/kg and 1.0 mg/kg, respectively.

2.3. Manufacturing process

Iron (II) taurate

The petitioner indicated that iron (II) taurate is manufactured by the addition of ferrous oxide or ferrous carbonate to taurine and subsequent crystallisation. Further details were not provided.

The petitioner indicated that it is possible to produce taurine using genetically modified microorganisms but the Panel concludes that these sources are not part of the present opinion because they would require a separate submission under Regulation (EC) No 1829/2003.

Magnesium taurate

One petitioner indicated that magnesium taurate is manufactured by the addition of a magnesium base to L-taurine and subsequent crystallisation. The other petitioner indicated that magnesium taurate is made by reaction of a magnesium source and taurine followed by selective drying.

Magnesium acetyl taurate

Magnesium acetyl taurate is prepared from magnesium hydroxide, taurine and acetic anhydride, essentially as described for the production of sodium N-acetyl taurinate (Terakoa *et al*., 1925).

2.4. Methods of analysis in food

Iron (II) taurate

The petitioner indicated that following appropriate extraction and preparation, iron (II) from iron (II) taurate can be analysed by Atomic Absorption Spectrometry (AAS) or Inductively Coupled Plasma (ICP) methods.

Magnesium taurate

One petitioner indicated that following appropriate extraction and preparation, AAS or ICP methods can be applied to determine magnesium. The other petitioner indicated that magnesium can be detected by Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES) methods.

Magnesium acetyl taurate

The petitioner indicated that acetyl taurate from magnesium acetyl taurate can be determined and quantified using HPLC with UV detection. Magnesium can be determined by existing AAS or ICP methods.

2.5. Reaction and fate in foods to which the source is added

Iron (II) taurate

The petitioner indicated that iron (II) taurate is stable in foods. Further data were not provided.

Magnesium taurate

One petitioner indicated that the product is stable in foods. The other petitioner indicated that the product is stable up to 3 years (<2 % degradation) and that there are no harmful degradation products. Further data were not provided.

Magnesium acetyl taurate

Magnesium acetyl taurate was shown to be stable in experiments which revealed that after 43 months under normal storing conditions at 22 ^{o}C, 93.2 % of the original amount was still present.

Taurate

Taurate can be determined after derivatisation with dabsylchloride by HLPC with UV detection (EFSA, 2009).

2.6. Case of need and proposed uses

Iron (II) taurate

Iron (II) taurate is to be used as a source of iron in food supplements that are in the form of tablets, caplets, capsules, chewable tablets, effervescent powders and liquids.

The petitioner indicated that the quantity of iron (II) taurate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply adults with up to 14 mg iron/day.

Magnesium taurate

Magnesium taurate is to be used as a source of magnesium in food supplements that are in the form of tablets, caplets, capsules, chewable tablets, effervescent powders and liquids.

Both petitioners indicated that the quantity of magnesium taurate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply adults with up to 250 mg magnesium/day.

Magnesium acetyl taurate

The petitioner indicated that magnesium acetyl taurate will be used in food supplements including for example tablets, powders and liquids.

The petitioner stated that the amount of 250 mg magnesium acetyl taurate would be taken 1 to 3 times a day.

2.7. Information on existing authorisations and evaluations

Iron

The Scientific Committee on Food (SCF) recommended daily intakes of 6 and 4 mg iron for infants aged 0.5-1 year and 1-3 years respectively, assuming 15% absorption of the daily intake. For adults, assuming 10% absorption, the recommended dietary iron intake has been estimated as between 8 and 10 mg iron/day (SCF, 1993).

In 2004, the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) of EFSA concluded that the available data were insufficient to establish a Tolerable Upper Intake Level (UL) for iron. Based on estimates of current iron intakes in European countries, the risk of adverse effects from a high iron intake from food sources, including fortified foods in some countries, but excluding supplements, is considered to be low for the population as a whole, except for those homozygous for hereditary haemochromatosis (up to 0.5% of the population). However, intake of iron from food supplements in men and postmenopausal women may increase the proportion of the population likely to develop biochemical

indicators of high iron stores. Some groups at special risk for poor iron status, such as menstruating women or children, could benefit from additional iron intake and/or an improved availability of dietary iron (EFSA, 2004).

The Expert Group on Vitamins and Minerals (EVM) (2003) concluded that there are insufficient appropriate data to establish a safe upper level for iron. It was also stated that for guidance purposes, a supplemental intake of approximately 17 mg/day (equivalent to 0.28 mg/kg bw/day for a 60 kg adult) would not be expected to produce adverse effects in the majority of people.

Fortification of food with iron is common in developing countries, where deficiency of the element is widespread. In the UK there is mandatory fortification of white and brown flour at a level not lower than 16.5 mg iron/kg flour. Many breakfast cereals are fortified on a voluntary basis; levels vary but are typically within the range of 70 to 120 mg iron/kg (EVM, 2003).

The German Federal Institute for Risk Assessment (BfR) (BfR, 2005) recommended that iron should no longer be used in food supplements. Targeted, individual iron substitution, which may be necessary because of specific indications like blood loss or absorption disorders, should only be done under medical supervision.

The Population Reference Intake (PRI) for iron for adults established by the SCF is 9 and 20 mg/day for males and females respectively, ranging from 4-20 mg/day depending on the age group (SCF, 1993).

Magnesium

For magnesium, the SCF (1993) determined an Acceptable Range of Intake for Adults of 150-500 mg/day.

The SCF has issued an opinion on the UL of magnesium (SCF, 2001). A UL of 250 mg magnesium/day from supplements was established based on a no-observed-adverse-effect-level (NOAEL) for a mild, transient laxative effect. This UL is applicable for adults, including pregnant and lactating women, and children aged 4 years and older (SCF, 2001).

The EVM could not establish a safe upper level for magnesium but provided a guidance level of 400 mg magnesium for supplemental use (EVM, 2003). This is equivalent to 6.7 mg/kg bw/day in a 60 kg adult.

The Food and Nutrition board (FNB, 1997) defined upper levels for magnesium for children older than 12 months and adults, varying from 65 mg supplemental magnesium for children aged 1- 3 years, to 350 mg supplementary magnesium for adolescents and adults.

Other salts of magnesium (e.g. magnesium citrate, gluconate, carbonate and chloride) have been approved for the use in the manufacture of food supplements and are listed in Annex II of Directive 2002/46/EC (EC, 2002).

The Population Reference Intake for magnesium for adults is 150-500 mg/day, ranging from 80-500 mg/day depending on the age group (SCF, 1993).

Taurate (taurine)

In 1999, the SCF expressed an opinion on caffeine, taurine and D-glucurono-γ-lactone as constituents of the so-called “energy” drinks.

For taurine the SCF was unable to conclude that the safety-in-use of taurine within the concentration ranges reported for these constituents in "energy" drinks had been adequately established. It indicated that further studies would be required to establish safe upper levels for daily intake of taurine.

In 2002, following the submission of new information by a manufacturer of "energy" drinks and the publication of relevant reports and statements by the Australian New Zealand Food Safety Authority and the UK Food Standard Agency, the SCF was asked by the European Commission to indicate if the conclusions of its 1999 opinion needed to be revised. On 5 March 2003, the SCF expressed an opinion on additional information on "energy" drinks.

Concerning taurine, the SCF indicated that the new 13-week study in rats provided further useful information and that it showed no significant changes in pathological measures, but it did show the occurrence of significant behavioural effects (increased activity and self-chewing), and possibly impaired motor performance, which could have been mediated via a pharmacological action on the central nervous system. In view of these findings, the SCF was of the opinion that focused neurological studies were needed. The SCF concluded that these effects should be taken into account in human risk assessment, noting that behavioural effects were observed at the lowest dose tested of 300 mg/kg bw/day. This effect level is 36-fold above the estimated human intake of taurine (8.3 mg/kg bw for a 60 kg adult) at the mean chronic daily intake for "energy" drinks, and 6-fold above the estimate for acute intake (50 mg/kg bw for a 60 kg adult). The absence of a NOAEL for these effects precludes the setting of a safe upper level for daily intake of taurine. The SCF's reservations were expressed in the context of an estimated acute intake of taurine of up to 3000 mg/day from consumption of "energy" drinks, compared with the highest estimated intake of taurine from naturally occurring sources in the diet of 400 mg/day.

Following these opinions, and taking into account the remarks made by the SCF, a manufacturer of "energy" drinks has submitted new data on the safety-in-use of taurine (and D-glucurono-γ-lactone) as constituents of the so-called "energy" drinks.

In a recent opinion the ANS Panel provided a review of the data submitted on the safety-in-use of taurine as constituents of the so-called "energy" drinks and provided a scientific opinion on the safety-in-use of taurine (and D-glucurono-γ-lactone) as constituents of the so-called "energy" drinks (EFSA, 2009).

It was concluded that the NOAEL derived from a new 13-week oral neurotoxicity study in male and female rats including functional observational battery (FOB) and locomotor activity tests confirmed the NOAEL established in the earlier 13-week study already described by the SCF in 2003 of 1000 mg taurine/kg bw/day – the highest dose tested, and provided evidence for a NOAEL of 1500 mg taurine/kg bw/day for behavioural effects. The results of this study were sufficient to address the previously raised concerns, notably the observation on increased activity and possible decrements in motor skills on the rotarod.

Given the fact that taurine is a natural body constituent, the Panel concluded that the margins of safety between the NOAEL of 1000 mg taurine kg bw/day and the mean and 97th percentile intake estimates from energy drinks estimated by the SCF (1999) to be 500 mg taurine (8.3 mg taurine/kg bw/day for a 60 kg person) and 1400 mg taurine/day (23.3 mg/kg bw/day for a 60 kg person) are sufficiently large to conclude that exposure to taurine at the levels mentioned is not of safety concern.

A daily requirement of taurine for humans has not been determined.

Acetyl taurate

No existing authorisation or evaluations are available.

2.8. Exposure

Iron (II) taurate

The iron content of food varies greatly, and factors such as the soil, climate conditions and processing can influence the iron content of similar foods. The amount of iron detected in food can vary due to differences in analytical methods. Foods rich in total iron include liver and offal, game and beef, cereals and cereal products; pulses also contain moderate to high levels. Poor sources of iron include milk and dairy products, whereas pork, poultry, and green vegetables contain intermediate concentrations (EFSA, 2004).

According to the SCF the average and 97.5th percentile iron intakes from food in European countries vary from 10 to 17 mg/day and 17 to 29 mg/day, respectively. Including the intake from food supplements high percentile values are in the range from 27 to 72 mg/day (SCF, 2003).

The petitioner indicates that the quantity of iron (II) taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 14 mg iron/day. This is equivalent to 76 mg iron (II) taurate providing 62 mg taurate. For a 60 kg adult the potential exposure to taurate would be 1.0 mg/kg bw/day.

Magnesium taurate

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts, generally have a higher magnesium content (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol do not contain magnesium. Meat, most kinds of fish, fruit, most vegetables and dairy products contain less than 250 mg magnesium/kg wet weight. Cacao and bitter chocolate, conches, shrimps, soybeans, butter beans, and beet greens contain over 1000 mg magnesium/kg. The magnesium content of grain and grain products largely depends on processing: high concentrations (1100-1800 mg/kg) are found in whole barley, whole rye or wheat flour or brown rice (EVM, 2003; SCF, 2001).

According to the SCF (2001), the average and 97.5th percentile magnesium intakes from food and supplements in European countries vary from 208 to 353 mg/person/day and 350 to 618 mg/person/day, respectively.

The quantity of magnesium taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 250 mg magnesium/day. The amount of 250 mg magnesium/day equals the UL of the SCF (2001). This 250 mg of magnesium will be provided by 2804 mg magnesium taurate providing 2554 mg taurate, equal to 43 mg/kg bw/day for a 60 kg person.

Magnesium acetyl taurate

The petitioner indicated that use levels of magnesium acetyl taurate in food supplements may amount to a dose of 250 mg magnesium acetyl taurate to be taken 1 to 3 times a day. This

amounts to 250 to 750 mg magnesium acetyl taurate/day providing 17 to 51 mg magnesium/day and 233 to 699 mg acetyl taurate/day, equal to 3.9 to 11.7 mg/kg bw/day for a 60 kg adult.

The Panel noted that the UL for supplemental magnesium as established by the SCF (2001) is 250 mg/day. To provide this amount, the supplement should contain about 3.7 g magnesium acetyl taurate corresponding to approximately 3.4 g acetyl taurate/day. In this case, the potential exposure to acetyl taurate would be 57 mg/kg bw/day for a 60 kg adult.

Taurate (taurine)

Taurine is present in animal products, but generally absent or present at trace levels in plant products. High levels of taurine (250- 850 mg per 100 g) are observed in some types of seafood (raw oyster, raw clam, raw mussel, raw scallop, raw squid, octopus, ink fish, crab). The amount of taurine in fish is variable (30-260 mg per 100 g). Beef, pork and veal (raw or broiled) contain taurine in concentrations ranging from 30-70 mg per 100 g. The taurine content found in turkey and chicken (raw, broiled and roasted) ranges from 10-380 mg per 100 g. The taurine content found in dairy products was less than that found in meat (0-9 mg per 100 mL). Amounts are given in mg per 100 g edible portion (Laidlaw, 1990; Pasantes-Morales, 1969).

Taurine can also be a constituent of the so-called "energy" drinks. In 2003 the SCF established a mean chronic consumption of “energy drinks” of 0.5 cans per person per day (250 mL per can) (SCF, 2003). High chronic exposure was estimated by the SCF to be 1.4 cans per person per day. This figure was based on the 95th percentile exposure of regular users, a group which represents 12% of the total population.

Based on the assumption that a can contains 250 mL and 4000 mg/L taurine, the SCF calculated that these values result in a mean daily exposure to 500 mg taurine, based on the consumption of 0.5 can, corresponding to 8.3 mg taurine/kg bw/day for a 60 kg person. The 95th percentile exposure for regular users, based on the consumption of 1.4 cans, would amount to 1400 mg taurine/day, corresponding to 23.3 mg/kg bw/day for a 60 kg person.

The previous opinion of the SCF also noted that for acute consumption 3 cans/day as a reasonable high consumption has been used, this amount being higher than the 90th percentile recorded in the Austrian survey (2.6 cans/day) and being the average reported in the Irish survey for the most number of cans consumed in a single session. The SCF also indicated that it was aware that amounts of up to 8-12 cans/day were reported by a few extreme consumers in both surveys.

The mean daily exposure to taurine from omnivore diets was determined to be around 58 mg (range from 9 to 372 mg) and to be low or negligible from a strict vegetarian diet (Rana and Sanders, 1986). In another study taurine exposure was estimated to be generally less than 200 mg/day, even in individuals eating a high meat diet (Laidlaw *et al.,* 1990) whereas according to Hayes and Trautwein (1994) taurine exposure was estimated to vary between 40 and 400 mg/day, amounting to 0.7 to 6.7 mg/kg bw/day for a 60 kg person.

In newborns, taurine is supplied almost completely by mother’s milk. The concentration of taurine in human milk tends to decrease during the early lactation period. Kim *et al.,* (1998) measured a concentration of 419 ± 156 nmol/mL on the first day after the start of milk secretion decreasing to 304 ± 94 nmol/mL on the 30th day. The intake by the breastfed infant progressively increased as a result of the increase in milk intake, from 3.0 ± 1.7 mg/day on the first day to 26.5 ± 4.9 mg/day on the 30th day (Kim *et al.*, 1998).

Taurine is added to most synthetic human infant formulas (about 50 mg/L) (Laidlaw, 1990) and paediatric parenteral solutions throughout the world (Sturman and Chesney, 1995).

The Panel notes that if in a multivitamin supplement all iron and magnesium at the above listed levels (conservative estimates) were to be provided as the taurate form this would result in a potential exposure of (1 mg/kg bw + 43 mg/kg bw) about 44 mg taurate/kg bw for a 60 kg person.

3. Biological and toxicological data

Biological and toxicological data on iron and magnesium have been evaluated by several authorities (CRN, 2004; EFSA, 2004; EVM, 2003; FNB, 1997; SCF, 2001).

The present opinion will focus on data for taurate and acetyl taurate since the safety of iron and magnesium, in terms of amounts that may be consumed, is outside the remit of this Panel.

3.1. Bioavailability of iron and magnesium from their iron (II) taurate and magnesium taurate and magnesium acetyl taurate sources

Iron (II) taurate

The petitioner indicated that the metabolic fate and biological distribution of iron (II) taurate is expected to be similar to that of other dissociable sources of iron in the diet because the source is expected to dissociate before absorption. It can be expected that iron (II) taurate readily dissociates into iron and taurate in the human body.

Magnesium taurate

The petitioners indicated that magnesium taurate readily dissociates into magnesium and taurine in the human body. Therefore the metabolic fate and biological distribution of magnesium taurate is expected to be similar to that of other dissociable sources of magnesium in the diet. Generally, magnesium is absorbed in an ionised form; there is no indication of either a directly coupled transport of magnesium with the uptake of other nutrients, or of significant absorption of magnesium complexes (Vormann, 2003).

The influence of different anions (sulphate, acetate, lactate, monohydrocitrate and ascorbate) on the absorption of magnesium ions has been studied in the rat small intestine in an *in vitro* absorption model. The author stated that the half absorption time – t ½ (connected with rate of absorption) – depends on the anion molecular weight and does not depend on the molecular weight of the whole magnesium salt. The absorption of magnesium ions from all salts reached its maximal value after 15 minutes. A negative correlation between molecular weight of the magnesium salt and the area under the curve was found (Ryszka, 1992).

Taurine (taurate)

Taurine (beta-amino ethane sulphonic acid) (taurate) is a naturally occurring beta-amino acid. Taurine is present in the diet and is a normal metabolite in humans. It is a metabolic product of sulphur amino acids, mainly biosynthesised from cysteine in the liver (SCF, 1999). It participates in the formation of bile salts and the detoxification of certain xenobiotics. It is

involved in a number of crucial physiological processes including modulation of calcium flux and neuronal excitability, osmoregulation, and membrane stabilisation (SCF, 1999).

Taurine is not incorporated into protein and in the body mainly occurs in the free form (O'Flaherty, 1997). In mammals, taurine is the major intracellular free amino acid in many tissues, including skeletal and cardiac muscle, and the brain (Huxtable, 1992; Sturman and Chesney, 1995). Whereas plasma taurine concentrations typically fall in the range of 50-200 µM (Sturman *et al*., 1975), the intracellular taurine content of taurine-rich tissues is maintained at 10-30 mM, implying an approximate 100-fold transmembrane taurine gradient that is achieved by active transport (McCarty, 1996).

In a whole-body autoradiography study in rats, taurine (intravenously injected) was rapidly eliminated from the blood stream almost regardless of the dosage level. The largest amount of radioactivity measured in the earlier periods was found in the kidney, liver and small intestine followed by the spleen and lungs; the least uptake was observed in the brain (Minato, 1969).

In general, amino acid uptake takes place in the small intestine, especially in the mid-lower jejunum. Transport occurs through simple or facilitated diffusion but, quantitatively, the majority occurs via carrier-mediated active transport (O'Flaherty, 1997). A number of carrier systems exist, each being responsible for the transport of a particular class of amino acids.

Research has established that enterocytes possess an efficient transport system for the uptake of taurine. There appear to be three carrier proteins involved in intestinal taurine uptake: a specific taurine carrier, a beta-amino acid carrier (shared by the beta-amino acids) and an imino acid carrier (imino = NH_2^+; amino = NH_3^+). The contribution that each carrier makes to intestinal transport varies from species to species (O'Flaherty, 1997). Activity seems to be greater in young developing animals than in adults, a consequence of the greater reliance on dietary taurine in the young as a result of immature taurine metabolism (O'Flaherty, 1997).

Taurine metabolism can be described by two exchangeable pools: a small (2 mmoles) rapid exchanging pool (t ½ about 0.1 hour) and a large (98 mmoles) very slowly exchanging pool (t ½ about 70 hours) (Sturman *et al*., 1975). Supplemental oral taurine enters the rapidly exchangeable pool (Thompson and Vivian, 1977). It causes a transient increase in plasma taurine levels and is excreted in urine without equilibration with the slowly exchangeable body pool that is primarily located in the muscles (Sturman *et al*., 1975). Because of the nearly quantitative recovery of supplemental taurine in urine, these authors suggest that body taurine pools cannot be expanded greatly by exogenous taurine (Sturman *et al*., 1975).

Taurine is excreted in two ways, but it is predominantly excreted in the urine (Sturman *et al*., 1975). Urinary taurine excretion in humans is related to the level of body taurine as well as to dietary intake (Thompson and Vivian, 1977). The taurine body pool size is largely regulated by the kidney (Sturman and Chesney, 1995). Taurine is readily eliminated in the urine if body taurine levels are adequate. However, in times of taurine depletion, the kidneys reabsorb taurine and do not allow it to be lost in the urine. This adaptive response has been localised to the proximal tubule brush border membrane, where the transporter activity is shared with other beta-amino acids and gamma-amino butyric acid (GABA) (Sturman and Chesney, 1995). These findings support a role for (renal) intracellular taurine as the influence of renal adaptation rather than a role for the extracellular, or plasma concentration (Sturman and Chesney, 1995). Taurine is also excreted in the bile, where it is bound to bile acids. Factors reported to influence the level of excretion in humans include age, hormones, radiation and stress (Thompson and Vivian, 1977).

Taurine is essential to newborns. Pre-term and term infants have very little, if any, capacity to synthesise the taurine necessary for their normal development. Adults normally make their own taurine, but the capacity for endogenous synthesis is limited in humans (particularly in infants). Since humans never developed a high level of cysteine sulfinic acid decarboxylase, an enzyme necessary for the formation of taurine from cysteine, people are probably somewhat dependent upon dietary taurine (Rana and Sanders, 1986). Dietary taurine intake may play an important role in maintaining body taurine pools (Laidlaw *et al*., 1990; Pasantes-Morales, 1989). Plasma, blood cell and/or urine taurine levels are reported to be decreased in newborn infants fed formulas lacking taurine, children and adults undergoing long-term total parenteral nutrition that does not provide taurine and adult vegans whose diet is devoid of measurable taurine (Stewart *et al.*, 1990).

Acetyl taurate

The petitioner indicated that the N-acetylation of the amine moiety of taurate in magnesium acetyl taurate modifies the polarity of the taurine molecule, making it more lipophilic enabling easier membrane passage (Bidri and Choay, 2003).

Data on the bioavailability of acetyl taurate were not provided. Data on its possible deacetylation to taurate or on possible N-acetylation of taurate to acetyl taurate were also not provided.

3.2. Toxicological data

Iron (II) taurate

Data on the acute or subchronic toxicity of iron (II) taurate were not provided.

Due to the expected dissociation of iron (II) taurate in the body before absorption, data on iron and taurate (or taurine) can be used to evaluate the safety of iron (II) taurate.

Magnesium taurate

Due to the expected dissociation of magnesium taurate in the body before absorption, data on magnesium and taurate (or taurine) can be used to evaluate the safety of magnesium taurate.

Magnesium acetyl taurate

Due to the expected dissociation of magnesium acetyl taurate in the body before absorption, data on magnesium and acetyl taurine can be used to evaluate the safety of magnesium acetyl taurate.

Iron

The safety of iron has been evaluated by several authorities (EFSA 2004; EVM, 2003).

The EFSA Opinion (EFSA, 2004) stated that adverse gastrointestinal effects (i.e. nausea, epigastric discomfort, constipation) have been reported after short-term daily oral dosage at 50-60 mg of supplemental non-haem iron preparations, particularly if taken without food. It was also concluded that an acute oral dose of 60 mg/kg bw can be lethal but that lower oral doses, about 10-20 mg iron/kg bw, do not cause acute systemic toxicity.

The EVM (2003) indicated that most cases of acute iron poisoning occur in children, due to accidental ingestion of iron supplements intended for adults. The acute toxic dose of iron in infants is considered to be approximately 20 mg/kg bw, associated with gastrointestinal irritation, whilst systemic effects do not generally occur at doses < 60 mg/kg bw. The lethal dose in children is approximately 200 – 300 mg/kg bw. Iron poisoning in adults is rare. Individual case reports suggest that a dose of approximately 100 g (approximately 1400 mg/kg bw) iron is lethal, although survival may occur with treatment.

The EVM (2003) evaluation also indicated that high doses of iron supplements are frequently associated with gastrointestinal effects, especially constipation, but also with nausea, diarrhoea and vomiting. The severity and occurrence of the effects depend on the formulation of the supplement and the amount of iron released in the stomach.

Supplementary doses of 100-200 mg iron/day and above have been associated with nausea, vomiting and epigastric pain. Other studies have reported a range of gastrointestinal effects, including diarrhoea, nausea, vomiting, constipation and epigastric pain, following supplementary doses of between 50 and 220 mg/day. However, such effects were variable and appeared to vary depending on the formulation of the iron supplement given, with fewer adverse effects reported by subjects given supplementary iron as chelated iron or haem iron than by subjects given ferrous sulphate (EVM, 2003 and references therein).

Magnesium

The safety of magnesium has been evaluated by several authorities (CRN, 2004; EVM, 2003; FNB, 1997; SCF, 2001).

The EVM (2003) concluded that the common effect of excessive ingestion of magnesium is osmotic diarrhoea. However, this effect was only observed in a limited number of studies of variable quality. There are only limited data on the oral and general toxicity of magnesium in animals. The available data suggest a lack of carcinogenicity at doses of up to 3000 mg/kg bw/day. Mutagenicity tests on magnesium salts have also been negative.

Key studies of high magnesium intake have been evaluated by the SCF in its Opinion on the UL of magnesium (SCF, 2001). In brief, the NOAEL for magnesium in supplements is 250 mg/day, and the LOAEL is 360/365 mg/day, with mild diarrhoea as the most sensitive non-desirable effect. Based on the NOAEL, the SCF established a UL of 250 mg supplemental magnesium per day, which applies to adults, including pregnant and lactating women, and children aged 4 years and older (SCF, 2001).

Taurate (taurine)

The petitioner indicated that the acute toxicity of taurine has been studied in dogs, mice, rabbits, rats and mammals (species unspecified). The petitioner also indicated that no (side)effects were mentioned upon intravenous, oral, intramuscular, intraperitoneal and/or subcutaneous administration of doses varying from 2-10 g/kg, except for one study (Kihara *et al*., 1991). In this study 7 g/kg (intravenous) or 5 g/kg (oral) taurine was administered to Wistar rats. No animals died during the observation period of 14 days upon both intravenous and oral administration. Upon intravenous administration, hyperuresis during the administration and slow deep breathing, decrease of spontaneous motor activity and piloerection were observed just after the administration in many animals including those in the control group. No abnormal clinical signs were observed during the observation period after the oral administration (Kihara *et al.,* 1991). As the mentioned (side)effects only

happened during intravenous administration and were seen in the test and also in the control group, the petitioner concluded that they may be the result of the stress of the injection.

Takahashi (1972) studied the long-term effect of high oral taurine intake in mice (5% (w/w) (intake from the diet about 6-7 g/kg bw/day) throughout three generations. Following this treatment no effect was seen on reproduction performance. The size of heart, lung and ovary in the third generation mice fed the taurine diet was significantly smaller, but histologically these organs showed no abnormalities. The other organs examined were all normal, both macroscopically and microscopically. Histologically spermatogenesis of taurine fed animal was superior to that of control animals (Takahashi, 1972).

Takahashi (1972) studied the teratology of taurine in mice. In this study taurine was administered orally to pregnant ICR mice at the daily level of 4 g/kg bw from the 7th day to the 14th day of gestation. No significant differences in implantation rate, and the number and body weight of off-spring born alive between treated and control animals were found. No visceral and skeletal malformations were observed in the foetuses of both groups (Takahashi, 1972).

Human studies with taurine intake are almost exclusively related to preventive and/or therapeutic purposes, and were not designed to study the safety of taurine.

In 2003 the SCF evaluated a newly submitted 13-week rat study with taurine at dose levels of 0, 300, 600 and 1000 mg/kg bw/day which showed no significant changes in pathological measures, but did show the occurrence of significant behavioural effects (increased activity and self-injury such as self-chewing), and possibly impaired motor performance, which could have been mediated via a pharmacological action on the central nervous system. In view of this, the SCF was of the opinion that focused neurological studies were needed. The absence of a NOAEL for these effects precluded the setting of a safe upper level for daily exposure to taurine.

The petitioner argued that there had been bias in the original study observations and the EFSA Working Group (EFSA, 2005) agreed that the observations reported in this study on certain behavioural patterns of the animals had not been well described in the original submission and could be discounted since there was no evidence of self-injury. However, the EFSA Working Group also concluded that, even combined with the expert analyses provided, this information was insufficient in itself to address all the concerns raised previously, notably the observation on increased activity and possible decrements in motor skills on the rotarod.

Therefore, the petitioner provided data from a specifically-designed, new 13-week oral (gavage and drinking water) neurotoxicity study of taurine in male and female rats which was performed according to FDA and OECD principles of Good Laboratory Practice. This study was evaluated by the ANS Panel in its opinion on taurine and D-glucurono-γ-lactone in "energy" drinks (EFSA, 2009). The objective of this study was to evaluate any potential neurotoxic effects of taurine when administered to rats for 13 weeks either by gavage or by way of drinking water, and to address the reliability of observations noted in the previous 13-week taurine toxicity study. Beginning in the second week of the acclimatisation period all animals (180 male and 180 female) were tested twice in the FOB and locomotor activity paradigms. After initial evaluations, outliers in locomotor activity were eliminated from the study. The remaining animals were randomised based on their performance on the rotarod test. Finally, the mean and standard deviation of the locomotor activity results were analysed to ensure that group means and variances were approximately equal before initiation of dosing thereby minimising subsequent skewing of these data. Potential functional deficits were assessed using a FOB and a measure of spontaneous locomotor activity. This study was

conducted in a "blinded" manner, in which the actual dose level for each group (gavage and drinking water) were unknown to the personnel conducting the study, in order to remove human bias from all aspects of the study.

Taurine in the vehicle, deionised water, was administered orally by gavage once daily for 13 weeks to 2 groups of 20 male and 20 female Cr1:CD(SD) rats at dose levels of 600 and 1000 mg/kg bw/day respectively. In addition, taurine was administered *ad libitum* in drinking water for 13 weeks to 2 groups of 20 male and 20 female Cr1:CD(SD) rats at target dose levels of 1000 and 1500 mg/kg bw/day (actual mean taurine intake levels obtained with drinking water were 1095 and 1117 mg/kg bw/day for the males and females respectively in the low dose group and 1647 and 1656 mg/kg bw/day for the males and females respectively in the high dose group). Concurrent control groups received the vehicle by gavage and drinking water respectively, on comparable regimes. Clinical examinations were performed daily and detailed physical examinations were performed weekly. These examinations were also conducted "blinded" with respect to treatment. Individual body weights and water consumption were recorded twice weekly and food consumption was recorded weekly. FOB and locomotor activity data were recorded for all animals prior to the initiation of dose administration and during study weeks 0, 6 and 12. Complete necropsies were conducted on all animals, and selected tissues and organs were collected at the scheduled necropsy.

The results indicated that there were no test-article-related deaths, clinical findings or macroscopic findings. No test-article-related effects were observed on body weights or food consumption. Some differences were observed in water consumption when rats were supplied taurine *ad libitum* in the drinking water. Increases in water consumption in the 1000 and 1500 mg/kg bw/day group males were noted only for study days 0 to 3 and/or 3 to 7 (both in g/animal/day and g/kg bw/day). The petitioner indicated that these differences were considered test-article-related, however they were not considered adverse, occurred temporarily and were considered to reflect adaptation to the osmotic property of the test-article.

There were no test-article-related effects on FOB parameters (home cage, handling, open field, sensory, neuromuscular and physiological observations). Locomotor activity counts (total and ambulatory) and patterns were unaffected by test-article administration.

Based on these results it was concluded that the oral administration of taurine at dose levels of 600 and 1000 mg/kg bw/day was well tolerated by male and female rats and did not result in any behavioural changes. The ANS Panel (EFSA, 2009) concluded that this study confirmed the NOAEL derived from the earlier study which included histopathology (1000 mg/kg bw/day – the highest dose tested). In addition, the study provided evidence of a NOAEL of 1500 mg/kg bw/day (actual level approximately 1650 mg/kg bw/day) for behavioural effects.

The SCF concluded that toxicological studies did not reveal any indication for a genotoxic, carcinogenic or teratogenic potential of taurine (SCF, 1999). They also indicated that there is no adequate study on chronic toxicity/carcinogenicity and that investigation of subacute/subchronic toxicity has also been fragmentary (SCF, 1999).

The ANS Panel concluded that new ADME data support the contention that oral exposure to taurine does not increase taurine levels in the brain, because in studies with rats brains taurine levels did not increase after dosage.

The ANS Panel also concluded that the NOAEL derived from the new 13-week oral neurotoxicity study in male and female rats including FOB and locomotor activity tests, confirmed the NOAEL of 1000 mg taurine/kg bw/day (the highest dose tested), established in

the earlier 13-week study described already by the SCF in 2003 and provided evidence for a NOAEL of 1500 mg taurine/kg bw/day for behavioural effects. The results of this study were sufficient to address the previously raised concerns (SCF, 1999), notably the observation on increased activity and possible decrements in motor skills on the rotarod.

Acetyl taurine

The petitioner provided data from acute toxicity studies in male mice with magnesium acetyl taurate demonstrating an oral LD_{50} of 17.4 g/kg bw. This toxicity was lower than the acute toxicity of $MgCl_2$ determined in the same series of experiments to be 7.60 g/kg bw. However, based on the amount of magnesium dosed to the animals, both magnesium salts appeared to be about equally toxic with an LD_{50} for magnesium taurate of 1186 mg magnesium/kg bw and that for $MgCl_2$ being 904 mg magnesium/kg bw.

The petitioner also reported that in a toxicity study with Sprague Dawley rats at oral dose levels of 250, 750 and 2250 mg magnesium acetyl taurate/kg bw for 3 months no effects on biochemical, haematological or urinary parameters were observed. Macroscopic and histopathological examinations did not show any adverse effect except for periportal liver lesions characterised by aggregation of mononuclear cells accompanied by a few necrotic hepatocytes in two out of 20 animals in the highest dose group. This is considered a frequent abnormality in animals of this strain and age (Greaves, 2000). Therefore the Panel concludes that the NOAEL in this study amounts to 2250 mg/kg bw, the highest dose tested.

4. Discussion

The present opinion deals only with the safety and bioavailability of particular sources of iron (II) and magnesium to be used in food supplements intended for the general population. The safety of iron and magnesium, in terms of amounts that may be consumed, is outside the remit of this Panel.

EFSA has issued an opinion on the UL for iron (EFSA, 2004). It was concluded that the available data were insufficient to establish a UL for iron. The opinion states that adverse gastrointestinal effects (i.e. nausea, epigastric discomfort, constipation) have been reported after short-term daily oral dosage at 50-60 mg of supplemental non-haem iron preparations, particularly if taken without food. It was also concluded that an acute oral dose of 60 mg/kg bw can be lethal, but that oral doses below about 10-20 mg iron/kg bw do not cause acute systemic toxicity.

The EVM (2003) also concluded that there are insufficient appropriate data to establish a safe upper level for iron. It was also stated that for guidance purposes, a supplemental intake of approximately 17 mg/day (equivalent to 0.28 mg/kg bw/day for a 60 kg adult) would not be expected to produce adverse effects in the majority of people.

The petitioner indicated that the quantity of iron (II) taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 14 mg iron/day. This amount is below the guidance value for supplemental intake proposed by the EVM (2003). A dose of 14 mg iron from iron (II) taurate is equivalent to 76 mg iron (II) taurate providing 62 mg taurate.

The petitioner indicated that it is possible that the taurine used in the manufacturing process may be produced using genetically modified microorganisms but the Panel concludes that

these sources are not part of the present opinion because they would require a separate submission under Regulation (EC) No 1829/2003.

The SCF has issued an opinion on the UL of magnesium (SCF, 2001). A UL of 250 mg supplemental magnesium per day was established based on a NOAEL for a mild, transient laxative effect. This UL is applicable for adults, including pregnant and lactating women, and children aged 4 years and older (SCF, 2001).

The Acceptable Range of Intake for adults was established at values between 150-500 mg/day (SCF, 1993).

The EVM (2003) concluded that there are insufficient data to establish a safe upper level for magnesium. Although a few studies reported mild and reversible diarrhoea in a small percentage of patients and healthy volunteers at levels of 384 to 470 mg/day, these symptoms were not observed in the majority of studies using similar or higher doses. For guidance purposes only, 400 mg/day supplemental magnesium would not be expected to result in any significant adverse effects. This is equivalent to 6.7 mg/kg bw/day in a 60 kg adult. Guidance has not been given for total magnesium since the reported adverse effects are not associated with magnesium in food.

The Food and Nutrition Board (FNB, 1997) defined upper levels for magnesium for children older than 12 months and adults, varying from 65 mg supplemental magnesium for children aged 1-3 years to 350 mg supplementary magnesium for adolescents and adults.

The petitioners for magnesium taurate indicated that the quantity of magnesium taurate to be added to food supplements is normally the quantity necessary to supply adults with up to 250 mg magnesium/day. The amount of 250 mg magnesium/day equals the UL of the SCF (2001). This 250 mg of magnesium will be provided by 2804 mg magnesium taurate providing 2554 mg taurine.

The petitioner for magnesium acetyl taurate indicated that use levels of magnesium acetyl taurate in food supplements may amount to a dose of 250 mg magnesium acetyl taurate to be taken 1 to 3 times a day. This amounts to 250 to 750 mg magnesium acetyl taurate/day providing 17 to 51 mg magnesium/day and 233 to 699 mg acetyl taurate/day.

The Panel noted that according to the SCF, the UL for magnesium is 250 mg/day. To provide 250 mg magnesium the supplement should contain about 3.7 g magnesium acetyl taurate, equal to approximately 3.4 g acetyl taurate/day.

Iron (II) taurate and magnesium taurate

Iron (II) taurate and magnesium taurate are readily soluble in water and from this the Panel concludes that the bioavailability of iron and magnesium from these sources is expected to be similar to that of other dissociable sources of iron and magnesium in the diet.

The exposure to taurine resulting from the proposed use and use levels of iron (II) taurate and magnesium taurate would amount to 62 + 2554 mg/day respectively = 2616 mg taurate/day, which would amount to approximately 44 mg taurine/kg bw/day for a 60 kg person. The SCF published an opinion on caffeine, taurine and D-glucurono-γ-lactone as constituents of so-called "energy" drinks in 1999 (SCF, 1999). This opinion stated that normal adult dietary intake of taurine is between 40 mg and 400 mg/day. Exposure to 2616 mg taurate/day would be significantly higher than this normal dietary intake.

Taurine (beta-amino ethane sulphonic acid) (taurate) is a naturally occurring beta-amino acid. Taurine is present in the diet and is a normal metabolite in humans (SCF, 1999). Taurine is

not incorporated into protein and occurs in the body mainly in the free form (O'Flaherty, 1997). Because of the nearly quantitative recovery of supplemental taurine in urine, Sturman *et al.* suggested that body taurine pools cannot be expanded greatly by exogenous taurine (Sturman *et al.*, 1975).

In 1999 and in 2003 the SCF expressed opinions on caffeine, taurine and D-glucurono-γ-lactone as constituents of the so-called "energy" drinks. In 2009 the ANS Panel of EFSA expressed an opinion on taurine and D-glucurono-γ-lactone in "energy" drinks.

The SCF already concluded in 1999 that toxicological studies did not reveal any indication for a genotoxic, teratogenic or carcinogenic potential of taurine (SCF, 1999 and references therein).

In 2003 the SCF evaluated a 13-week rat study with taurine at dose levels of 0, 300, 600 and 1000 mg/kg bw/day, which showed no significant changes in pathological parameters, but did show the occurrence of significant behavioural effects (increased activity and self-chewing), and possibly impaired motor performance, which could have been mediated via a pharmacological action on the central nervous system. In view of this, the SCF was of the opinion that focused neurological studies were needed and that the absence of a NOAEL for these effects precluded the setting of a safe upper level for daily exposure to taurine.

The ANS Panel (EFSA, 2009) evaluated a new 13-week oral toxicity and neurotoxicity study in male and female rats which included FOB and locomotor activity tests. The new study confirmed the NOAEL of 1000 mg/kg bw /day established in the earlier 13-week study previously described by the SCF in 2003 and provided evidence for a NOAEL of 1500 mg/kg bw/day for behavioural effects. The results of this study were considered to be sufficient to address the previously raised concerns, notably the observation on increased activity and possible decrements in motor skills on the rotarod. This NOAEL of at least 1000 mg/kg bw/day is 23-fold higher than the estimated combined exposure to taurine from use levels proposed for iron (II) taurate and magnesium taurate.

Given the facts that the NOAEL was the highest dose tested and that taurine is a natural body constituent, the Panel concludes that this margin of safety is sufficient. The Panel recognises that the major exposure to taurine (2554 mg) would come from the use of magnesium taurate as a source of magnesium as compared to exposure to only 62 mg taurine resulting from the proposed use levels of iron (II) taurate.

The margin of safety for the daily exposure to 62 mg taurate (equal to approximately 1 mg/kg bw/day for a 60 kg person) resulting from the proposed use levels of iron (II) taurate would be almost 1000 and based on this margin of safety the Panel concludes that the use of iron (II) taurate as a source of iron is not of safety concern.

The margin of safety for the intake of 2554 mg taurate (equal to 42.6 mg/kg bw/day for a 60 kg person) resulting from the proposed use of magnesium taurate up to dose levels of 250 mg magnesium a day would be 23. The Panel concludes that this margin of safety is sufficient and that the use of magnesium taurate as a source of magnesium at the proposed use levels is not of safety concern.

The Panel notes that in addition to the diet and supplement sources evaluated in this Opinion "energy" drinks can also be an important source of taurine (taurate). Combined intake of taurine from magnesium taurate and iron taurate from supplements at the proposed use levels, from "energy" drinks at the mean intake of 8.3 mg/kg bw/day and from the diet at 0.7 to 6.7 mg/kg bw/day would result in an exposure of 52.6 to 58.9 mg taurate/kg bw/day for a 60 kg person, resulting in a margin of safety of 17 to 19. Given the facts that the NOAEL was the

highest dose tested and that taurine is a natural body constituent, the Panel concludes that also this margin of safety is sufficient.

Magnesium acetyl taurate

Magnesium acetyl taurate is readily soluble in water and from this the Panel concludes that the bioavailability of magnesium from these sources is expected to be similar to that of other dissociable sources of magnesium in the diet.

Use of magnesium acetyl taurate at the proposed use levels would result in exposure 233 to 699 mg acetyl taurate/day, equal to 3.9 to 11.7 mg acetyl taurate/kg bw/day, and 17 to 51 mg magnesium/day for a 60 kg person.

The Panel notes that the proposed use levels of magnesium acetyl taurate would result in exposure to magnesium at a level below the UL of 250 mg magnesium per day for supplement use established by the SCF.

In the case that 250 mg magnesium will be provided as magnesium acetyl taurate, the potential exposure to acetyl taurate would be approximately 57 mg/kg bw/day.

The Panel notes that the toxicological database on acetyl taurine is limited. A 3-month oral toxicity study in rats reveals a NOAEL of 2250 mg/kg bw/day. Comparison of this NOAEL to the intake of acetyl taurate that would result from the proposed use levels of magnesium acetyl taurate of 3.9 to 11.7 mg acetyl taurate/kg bw/day results in a margin of safety of 192 to 577. . Given that the compound is an acetylated form of taurine and may thus represent a normal endogenous metabolite of taurine and the fact that the compound does not contain a structural alert for genotoxicity, the Panel considers this margin of safety adequate and concludes that the use of magnesium acetyl taurate as a source of magnesium at the proposed levels of use is not of safety concern.

CONCLUSIONS

The Panel concludes that the bioavailability or iron and magnesium from iron (II) taurate, magnesium taurate and magnesium acetyl taurate is expected to be similar to that of other dissociable sources of iron and magnesium in the diet.

The Panel concludes that that the use of iron (II) taurate, magnesium taurate and magnesium acetyl taurate as sources for iron and magnesium at the proposed use levels is not of safety concern.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier on Iron (II) Taurate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association.
2. Dossier on Magnesium taurinate (taurate). June 2005. Submitted by Vital Cell Life (VCL).

3. Dossier on Magnesium Taurate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. June, 2005. Submitted by Health Food Manufacturers Association.

4. Dossier de soumission pour l'évaluation de l'acétyl taurinate de magnésium comme ingrédient dans les compléments alimentaires selon la guidance du SCF/CS/ADD/NUT/21 Final. July 2001. Submitted by Laboratoire Unda SA.

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GLOSSARY / ABBREVIATIONS

AAS	Atomic Absorption Spectroscopy
ADME	Absorption, Distribution, Metabolism, and Excretion
AFC	Scientific Panel on food additives, flavourings, processing aids and materials in contact with food.
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
bw	body weight
CAS	Chemical Abstract Service
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
FDA	Food & Drug Administration
FOB	Functional Observational Battery
GABA	Gamma-Amino Butyric Acid
HPLC	High Performance Liquid Chromatography
ICP	Inductively Coupled Plasma
ICP-OES	Inductively Coupled Plasma-Optical Emission Spectroscopy
IOM	Institute of Medicine
LD_{50}	Lethal Dose, 50% i.e. dose that causes death among 50 % of treated animals
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
NOAEL	No-Observed-Adverse-Effect Level
OECD	Organisation for Economic Co-operation and Development
SCF	Scientific Committee on Food
UL	Tolerable Upper Intake Level
UV	Ultraviolet