European Food Safety Authority

The EFSA Journal (2009) 1088, 1-25

SCIENTIFIC OPINION

Calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate magnesium succinate and potassium malate added for nutritional purposes to food supplements [1]

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

(Question No EFSA-Q-2005-131, EFSA-Q-2005-136, EFSA-Q-2005-137, EFSA-Q-2005-141; EFSA-Q-2006-230; EFSA-Q-2008-025)

Adopted on 13 May 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission to the European Food Safety Authority (EFSA), the Scientific Panel on Additives and Nutrient Sources (ANS) added to Food was asked to provide a scientific opinion on the safety of calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate and potassium malate added for nutritional purposes as sources of calcium, magnesium and potassium in food supplements and on the bioavailability of magnesium, calcium and potassium from these sources.

Although no data were provided by the petitioners, human and animal studies indicate that magnesium and calcium are readily absorbed from orally ingested soluble organic salts. The Panel expects the bioavailability of calcium from the less soluble pyruvate and succinate salt sources to be comparable to that of readily soluble salts, given that the absorption of calcium from the gastrointestinal tract is primarily determined by food components, especially organic

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate magnesium succinate and potassium malate added for nutritional purposes to food supplements following a request from the European Commission. The *EFSA Journal* (2009) 1088, 1-25.

acids. Similarly, potassium from potassium malate is readily absorbed from the gastrointestinal tract.

No data were provided on the metabolic fate of calcium, magnesium, potassium, succinate, pyruvate, acetate and malate. However, the Panel noted that succinate, pyruvate, acetate and malate are normal constituents of the body with well documented biochemical fates in the Krebs cycle or the glycolytic pathway.

No specific toxicological data were provided by the petitioners on the succinate, pyruvate and acetate salts of calcium or magnesium. No specific toxicological data were provided by the petitioner on the malate salt of potassium. Studies that have investigated the effect of calcium pyruvate supplementation (daily doses of 13-25 g calcium pyruvate for 6 weeks in hyperlipidaemic subjects) during physical training, on body fat and metabolic responses to exercise did not describe any adverse effects, except for one study where adverse changes in serum lipid composition were documented following administration of 10 g daily for 30 days. DL-malic acid and potassium malate are permitted food additives with the numbers E296 and E351, respectively. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated malic acid and derived, on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food by adults, a group Acceptable Daily Intake (ADI) not specified for DL-malic acid and potassium DL-malate.

The petitioner for calcium succinate and calcium pyruvate proposes that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be up to 800 mg calcium/day. The petitioner for calcium acetate proposes its use as tablets containing 110 mg or 167 mg calcium; however, it is not clear from the dossier what the proposed daily exposure to calcium acetate would be. The Panel considered, as for others calcium sources, (calcium succinate or calcium pyruvate) that the quantity of calcium to be added to food supplements as calcium acetate will be also estimated to provide up to 800 mg calcium/day.

In the case of the 97.5 percentile European dietary calcium intakes for the adult population, the Panel noted that the total anticipated exposure to calcium from users of calcium succinate, calcium pyruvate or calcium acetate supplements with the proposed use levels may exceed the Tolerable Upper Intake Level (UL) defined by the Scientific Committee on Food (SCF) of 2500 mg/day.

The UL for magnesium supplements, as defined by the SCF, for adults is 250 mg/day. The petitioner states that the quantity of magnesium succinate or magnesium pyruvate 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.

No UL has been established for potassium, but it was stated by EFSA's Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) that long-term supplementary intake of up to 3 g/day, in addition to intake from food, has been shown not to have an adverse effect in adults. The petitioner proposes that the quantity of potassium malate to be added to food supplements will supply up to 350 mg potassium/day.

No ULs have been established by the SCF for succinate, pyruvate, acetate and malate. Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the maximum exposure to succinate, pyruvate and acetate from the respective sources as proposed by the petitioners would be 2, 3.4 and 2.4 g/day, respectively. The maximum exposure to malate from potassium malate would be 1.5 g/day. Combined intake of succinate and pyruvate salts from the proposed sources of calcium and magnesium would

increase the exposure to these anions to 3.2 and 5.2 g/day, respectively. No adverse effects have been reported for the proposed use levels for succinate, acetate and malate. A daily exposure of up to 46 g pyruvate has been shown in two studies to have no adverse effects although one study reported an increase in fasting serum levels of very low density lipoproteins and triglycerides in subjects exposed to 10 g pyruvate/day.

The Panel concludes the following:

- Calcium is expected to be bioavailable from the three sources of calcium (calcium succinate, calcium pyruvate and calcium acetate) to be used as nutritional substances in food supplements;
- Magnesium is expected to be bioavailable from the two sources of magnesium (magnesium succinate and magnesium pyruvate) to be used as nutritional substances in food supplements;
- Potassium is expected to be bioavailable from potassium malate which is to be used as a nutritional substance in food supplements;
- The use of calcium acetate, calcium succinate, calcium pyruvate, magnesium succinate, magnesium pyruvate and potassium malate, as sources of calcium, magnesium and potassium, in food supplements for the uses and at the use levels proposed by the petitioners is not of safety concern, provided that the UL for intake of the cations is not exceeded. However, the Panel noted that when the dietary intake is also taken into consideration, with supplementation of calcium succinate, calcium pyruvate or calcium acetate at the proposed daily use levels of up to 800 mg calcium, the UL defined by the SCF for calcium would be exceeded for the 97.5 percentile European adult population;
- The intake of pyruvate, succinate, malate and acetate from the corresponding sources is not of safety concern.

Key words:

Food supplements, foods, magnesium succinate, magnesium pyruvate, calcium pyruvate, calcium succinate, calcium acetate, potassium malate, CAS Registry Numbers 556-32-1, 140-99-8, 18983-79-4, 52009-14-0, 62-54-4, 585-09-1.

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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 magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate 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 magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate added for nutritional purposes in food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group A on Food Additives and Nutrient Sources of the ANS Panel for the preparation of this opinion: F. Aguilar, N. Bemrah, P. Galtier, J. Gilbert, S. Grilli, R. Guertler, G.E.N. Kass, C. Lambré, J.C. Larsen, J.-C. Leblanc, A. Mortensen, I. Pratt, I. Stankovic.

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

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate and potassium malate added for nutritional purposes in food supplements and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium and potassium themselves, in terms of the amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Magnesium succinate

The molecular formula of magnesium succinate is $MgC_4H_4O_4$, its molecular weight is 140.39 g/mol and its CAS Registry Number is 556-32-1 (Technical dossier, 2005a).

Synonyms proposed by the petitioner are magnesium butanedioate, and butanedioic acid magnesium salt.

Calcium succinate

The molecular formula of calcium succinate is $CaC_4H_4O_4$, its molecular weight is 140.4 g/mol and its CAS Registry Number is 140-99-8 (Technical dossier, 2005b).

The synonym proposed by the petitioner is butanedioic acid calcium salt.

Magnesium pyruvate

The molecular formula of magnesium pyruvate is $MgC_6H_6O_6$, its molecular weight is 198.4 g/mol and its CAS Registry Number is 18983-79-4 (Technical dossier, 2005c).

The synonym proposed by the petitioner is pyruvic acid magnesium salt.

Calcium pyruvate

The molecular formula of calcium pyruvate is $CaC_6H_6O_6$, its molecular weight is 214.2 g/mol and its CAS Registry Number is 52009-14-0 (Technical dossier, 2005d).

The synonym proposed by the petitioner is pyruvic acid calcium salt.

Calcium acetate

The molecular formula of calcium acetate is $CaC_4H_6O_4$, its molecular weight is 158.2 g/mol and its CAS Registry Number is 62-54-4 (Technical dossier, 2005e).

The synonym proposed by the petitioner is acetic acid calcium salt.

Potassium D,L-malate

The molecular formula of potassium malate is $K_2C_4H_6O_5$, its molecular weight is 210.3 g/mol and its CAS Registry Number is 585-09-1 (Technical dossier, 2008).

The synonyms proposed by the petitioner include the following: hydroxiethane-1,2-dicarboxylic acid potassium salt, malic acid potassium salt, hydroxybutanodioic acid dipotassium salt, and potassium α-hydroxysuccinate.

2.2. Specifications

The petitioner stated the following on the specifications:

Magnesium succinate

Magnesium succinate is a white powder that is soluble in water, its purity is not less than 97.0% and the total magnesium content is 17.3% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

Calcium succinate

Calcium succinate is a fine white powder, with a characteristic odour, that is slightly soluble in water. Its purity is not less than 97.0% and the total calcium content is 28.5% (based on theoretical calculations). The petitioner states that the source exists as calcium succinate monohydrate. The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

Magnesium pyruvate

Magnesium pyruvate is a white powder that is soluble in water. Its purity is not less than 98.0% and the total magnesium content is 12.2% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

Calcium pyruvate

Calcium pyruvate is a white to off-white powder that is slightly soluble in water. Its purity is not less than 97.0% and total calcium content is 18.7% (based on theoretical calculations). The petitioner states that the source exists as hydrated calcium pyruvate ($CaC_6H_6O_6$ 2.5 H_2O). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

Calcium acetate

Calcium acetate is a white powder that is freely soluble in water and slightly soluble in ethanol. The content of calcium acetate is not less than 99.0% and not more than 100.5%, and the total calcium content is 25.3% (based on theoretical calculations). The limits for impurities are as follows: chlorides 0.05%, fluorides 0.005%, sulphates 0.06%, arsenic not more than 3 mg/kg, lead not more than 10 mg/kg and heavy metals not more than 25 mg/kg.

Potassium D,L-malate

Potassium D,L-malate is a white powder that is soluble in water. Its purity is not less than 97.0% and total potassium content is 18.6% (based on theoretical calculations). The reported limits for impurities are as follows: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and mercury not more than 1 mg/kg.

The Panel notes that according to Commission Regulation (EC) No 629/2008 the maximum levels of lead, mercury and cadmium in food supplements as sold should be 3 mg/kg, 0.1 mg/kg and 1 mg/kg, respectively (EC, 2008).

2.3. Manufacturing processes

Magnesium succinate

Magnesium succinate is synthesised from magnesium carbonate and succinic acid.

Calcium succinate

Calcium succinate is synthesised from a calcium salt (identity not specified by petitioner) and succinic acid.

Magnesium pyruvate

Magnesium pyruvate is synthesised by the reaction of a magnesium carbonate with pyruvic acid.

Calcium pyruvate

Calcium pyruvate is synthesised by the reaction of a soluble calcium salt (identity not specified by petitioner) with pyruvic acid.

Calcium acetate

Calcium acetate is precipitated by the reaction of acetic acid and calcium hydroxide.

Potassium D,L-malate

Potassium D,L-malate is synthesised by the reaction of potassium hydroxide with D,L-malic acid.

2.4. Methods of analysis in food

Magnesium succinate, magnesium pyruvate, calcium succinate and calcium pyruvate

The petitioner listed AAS and ICP-AES as instrumental techniques for the determination of the food content of magnesium and calcium after appropriate extraction and preparation.

Calcium acetate

The petitioner described a titration method with calcon carbonic acid as an indicator.

Potassium D,- malate

The petitioner did not provide any analytical methods.

Succinate, pyruvate, acetate and malate anions of the sources

The petitioner did not provide any analytical methods.

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

Magnesium succinate and magnesium pyruvate, calcium succinate, calcium pyruvate, calcium acetate and potassium malate are described by the petitioners as stable in foods. However, no specific information was provided.

2.6. Case of need and proposed use levels

Calcium acetate, calcium pyruvate, calcium succinate, magnesium pyruvate, magnesium succinate, and potassium malate are intended to be used as sources of the respective nutrient cations.

The petitioners proposed the following uses for each of the salts:

Magnesium succinate, magnesium pyruvate, calcium succinate, calcium pyruvate and potassium malate are to be used by food supplement manufacturers as ingredients in tablets, caplets, capsules, chewable tablets, effervescent powders and liquids that are food supplements. Calcium acetate is proposed only to be used in tablet form. The method of incorporation of the source into the nutrient supplement is determined by the individual manufacturers as appropriate for the particular type of finished products.

The petitioners for calcium succinate and calcium pyruvate state that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be determined by individual formulators, but it is normally the quantity necessary to supply up to 800 mg calcium/day. The petitioner for calcium acetate proposes its use as tablets containing 110 mg or 167 mg calcium although no specification for the use levels as a food supplement was provided. The Panel considered that as for others calcium supplements (calcium succinate and calcium pyruvate), the quantity of calcium to be added to food supplements as calcium acetate will be determined by individual formulators, but it is normally the quantity necessary to supply up to 800 mg calcium/day

The petitioner states that the quantity of magnesium succinate or magnesium pyruvate 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. The petitioner states that the quantity of potassium as potassium malate to be added to food supplements will be determined by individual formulators but it is normally the quantity necessary to supply up to 350 mg potassium/day.

2.7. Information on existing authorisations and evaluations

Calcium acetate and potassium malate are permitted food additives with the numbers E263 and E351, respectively. Calcium acetate is licensed in Germany as a medical product.

The SCF established a Tolerable Upper Intake Level (UL) for calcium from all sources of 2500 mg/day for adults, and pregnant and lactating women (SCF, 2003). In 2001, the SCF established a UL for magnesium from supplements of 250 mg/day for adults (SCF, 2001).

The SCF has issued an opinion on the UL of potassium (EFSA, 2005b). No UL could be established for potassium but it was stated by EFSA's Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) that long-term supplementary intake of up to 3 g/day, in addition to intake from foods, has been shown not to have an adverse effect.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated malic acid and derived, on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food, a group Acceptable Daily Intake (ADI) not specified for DL-malic acid and sodium, potassium and calcium DL-malate (JECFA 1980, 1986). The SCF agreed with this group ADI for adults (SCF, 1990), but considered only the L-isomer acceptable for use in foods prepared for infants and young children (SCF, 1992).

The Scientific Panel on Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) evaluated a citrate malate source of calcium (EFSA, 2007) and concluded that its use as source of calcium in foods for Particular Nutritional Uses (PARNUTS) and foods for the general population (including food supplements) is of no safety concern.

The Population Reference Intake (PRI) for adults are in the order of 3.1-3.5 g/day for potassium, for calcium 700 mg/day (range 400-1200 mg/day depending on age), and for magnesium in the order of 150-500mg/day depending on age (SCF, 1993; SCF, 2001).

2.8. Exposure

This section deals with the calcium intake and anticipated exposure to succinic acid, pyruvic acid and acetic acid from calcium succinate, calcium pyruvate and calcium acetate, magnesium intake and anticipated exposure to succinic acid and pyruvic acid from magnesium succinate or magnesium pyruvate, and potassium intake and anticipated exposure to malic acid from potassium malate.

The body synthesises succinic acid, pyruvic acid and malic acid during the process of metabolising carbohydrates to energy. Some berries and some food products contain succinic acid, specifically those, whose preparation involves anaerobic processes. However, many everyday food products are devoid of succinic acid. Additional exposure comes from the use of succinic acid esters in food supplements (e.g. vitamin E acid succinate), as flavouring agents (e.g. succinic acid monomethyl ester) and also a small amount can come from carbohydrates produced in the gut. However, no data on total dietary exposure to succinate are available. Pyruvate is readily found in foods, including apples, beer and red wine, with concentrations up to 7 mg/100g (Souci *et al.,* 2008) but the daily amount consumed through an average diet is difficult to quantify. In addition, pyruvate supplements providing up to 2 g per tablet are readily available. It is also difficult to quantify the daily amount of malate consumed through an average diet as it is present in many foods and sold in many supplements. Concentrations typically ranging from 0.1 to 2 g/100g have been detected in fruits and wines (Antonelli *et al.,* 2008; Souci *et al.,* 2008) and the daily human consumption

of malic acid from vegetables, fruits and their juices is calculated to be in the order of 1.5 to 3 g (JECFA, 1966). Acetate is synthesised by the body and is present in many foods. The amount of acetate present in 1 g of calcium acetate is equivalent to 15 mL vinegar. This amount of acetate is rapidly metabolised to water and carbon dioxide. Overall, the total consumption of succinic acid, pyruvic acid, acetic acid and malic acid by the general population is difficult to assess.

2.8.1. Exposure to calcium succinate, calcium pyruvate and calcium acetate

Foods particularly rich in calcium are milk (1200 mg/kg), cheese (730-12000 mg/kg) and other dairy products (except butter), green leafy vegetables (except spinach), soybean products, bread and other baked goods made from calcium fortified flour (variable levels), almonds (2400 mg/kg), brazil nuts (1700 mg/kg) and hazelnuts (1400 mg/kg). In European diets 45 to 70% of calcium intake is from milk and dairy products (SCF, 2003).

According to the SCF and the UK Total Diet Study, the average and high percentile calcium intakes from food for adults in European countries vary from 683 to 944 mg/day and from 1308 to 1970 mg/day, respectively (SCF, 2003; Ysart *et al.*, 1999).

Table 1 summarises the information on calcium intake from food in European countries, anticipated exposure to calcium by using supplements as proposed by the petitioners, and ULs.

The Panel noted that the additional exposure of 800 mg of calcium/day from the proposed use of calcium succinate, calcium pyruvate and calcium acetate in food supplements would result in an anticipated total average exposure for adults of 1483 to 1744 mg/day and at the high percentile, a total exposure for adults of 2108 to 2770 mg/day.

Assuming a mean dietary calcium intake for children in Europe in the range of 804 to 809 mg/day and a high percentile intake range of 1338 to 1442 mg/day, the Panel estimated that daily consumption of an additional food supplement containing 800 mg calcium/day would result in a total anticipated exposure between 1604 and 1609 mg/day at the average level and a total anticipated exposure between 2138 and 2242 mg/day at the high level.

Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the equivalent intake of succinic, pyruvic and acetic acid would be 2, 3.4 and 2.4 g/day, respectively. Except for the pyruvate salts, used at high levels by athletes and body builders (their potential pyruvate intake may be up to 46 g/day (Stanko *et al.*, 1992), no potential high intake groups have been identified.

Table 1. **Summary information on calcium intake and anticipated exposure to succinic acid, pyruvic acid and acetic acid from calcium succinate/pyruvate/acetate**

Nutrient: calcium	**Intake (mg/day)**		**References**
Recommended Intake for adults	700		SCF, 1993
Recommended Intake for children	500-800 (up to 7 years) 1200-1300 (older children and adolescents)		SCF, 2003
Tolerable Upper Intake Level for adults (including pregnant and lactating women)	2500		SCF, 2003
Tolerable Upper Intake Level for children	Insufficient data		SCF, 2003
Nutrient: Calcium	**Average intake (mg/day)**	**High intake (95th or 97.5th) (mg/day)**	**References**
Intake range from food in Europe for adults	683-944	1308-1970	SCF, 2003; Ysart *et al.*, 1999
Intake range from food in Europe for children (3-17 years)	804-809	1338-1442	SCF, 2003; AFSSA, 2009
Amount of calcium added to supplements from calcium succinate/pyruvate/acetate as indicated by the petitioners	800	800	Technical dossier, 2005b; Technical dossier, 2005d ; Technical dossier, 2005e
Source: Calcium succinate/pyruvate/acetate			
Total anticipated exposure to calcium from supplement and food intake[1] for adults.	1483-1744	2108-2770	calculation by Panel
Total anticipated exposure to calcium from supplement and food intake[2] for children (3-17 years).	1604-1609	2138-2242	calculation by Panel

[1]calculation based on proposed use level of 800 mg/day plus average dietary intake of 683-944 mg/day and high dietary intake of 1308-1970 mg/day for adults

[2]calculation based on proposed use level of 800 mg/day plus average dietary intake of 804-809 mg/day and high dietary intake of 1338-1442 mg/day for children

2.8.2. Exposure to magnesium succinate and magnesium pyruvate

Magnesium is ubiquitous in foods, but its content varies substantially. Leafy vegetables, as well as grains and nuts, generally have higher magnesium contents (60-2700 mg/kg) than meats and dairy products (less than 280 mg/kg). Fats, refined sugars and pure alcohol are free of magnesium. Meat, most kinds of fish, fruit, most vegetables and dairy products contain less than 250 mg magnesium/kg. 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, the average and the 97.5 percentile of magnesium intakes from food for adults in European countries vary from 208 to 353 mg/day and from 350 to 628 mg/day, respectively (SCF, 2001). In children, the average and the 97.5 percentile of magnesium intakes from food vary from 196 to 227 mg/person/day and from 298 to 387 mg/day, respectively (AFSSA, 2009; SCF, 2001).

Table 2 summarises the information on magnesium intake from food in European countries, anticipated exposure to magnesium by using supplements as proposed by the petitioner and ULs.

Table 2. **Summary information on magnesium intake and anticipated exposure to succinic acid and pyruvic acid from magnesium succinate or magnesium pyruvate.**

Nutrient: Magnesium	**Intake (mg/day)**		**References**
Acceptable range of intake for adults	150-500		SCF, 1993
Tolerable Upper Intake Level for adults and children from 4 years on	250*		SCF, 2001
Nutrient: Magnesium	**Average intake (mg/day)**	**High intake (95^{th} or 97.5^{th}) (mg/day)**	**References**
Intake range from food in Europe for adults	208-353	350-628	SCF, 2001
Intake range from food in Europe for children (3-17 years)	196-227	298-387	SCF, 2001; AFSSA, 2009,
Amount of magnesium added to supplements from succinate/pyruvate as indicated by the petitioner	250	250	Technical dossier, 2005a; Technical dossier, 2005c
Source: Magnesium succinate/pyruvate			
Total anticipated exposure to magnesium from supplement and food intake[1] for adults.	458-603	600-878	calculation by Panel
Total anticipated exposure to magnesium from supplement and food intake[2] for children (3-17 years).	446-477	898-1265	calculation by Panel

* This UL is established for readily dissociable magnesium salts and compounds like magnesium oxide and does not include magnesium normally present in foods and beverages

[1] calculation based on proposed use level of 250 mg/day plus average dietary intake of 208-353 mg/day and high dietary intake of 350-628 mg/day for adults

[2] calculation based on proposed use level of 250 mg/day plus average dietary intake of 196-227 mg/day and high dietary intake of 297.8-387.4 mg/day for children

The Panel noted that the additional exposure of 250 mg of magnesium/day from the proposed use of magnesium succinate and magnesium pyruvate in food supplements would result in an anticipated total average exposure for adults ranging from 458 to 603 mg/day and at the high percentile of 600 to 878 mg/day.

The Panel estimated that daily consumption of an additional food supplement containing 250 mg magnesium/day would result in a total anticipated exposure for children between 446 to 477 mg/day at the average level and a total anticipated exposure between 898 to 1265 mg/day at the high level.

Based on an anticipated intake of 250 mg magnesium/day in food supplements, as indicated by the petitioner, the equivalent intake of succinic and pyruvic acid would be 1.2 and 1.8 g/day, respectively.

2.8.3. Exposure to potassium malate

Important potassium sources include potatoes, fruit and berries, vegetables, milk products (excluding cheese) and nuts. Potassium occurs in foods, mainly associated with weak organic acids. Potassium is also found in mineral, spring, and table waters, but the content varies considerably. Some mineral waters available on the market can, when consumed in large quantities, contribute significantly to the daily intake of potassium.

The average and the 97.5 percentile of potassium intakes from food for adults in European countries vary from 2.7 to 4.4 g/day and from 4.2 to 5.5 g/day, respectively (EFSA, 2005b). In children, the average and the 97.5 percentile of potassium intakes from food vary from 2.1 to 3.0 g/day and from 2.4 to 4.4 g/day, respectively (EFSA, 2005b)

Table 3 summarises the information on potassium intake from food in European countries, anticipated exposure to potassium by using supplements as proposed by the petitioner and ULs. The Panel noted that the additional exposure of 0.35 g of potassium/day from the proposed use of potassium malate in food supplements would for adults, result in an anticipated total average exposure of 3.05-4.35 g/day and an anticipated total exposure of 4.55-5.85 g/day at the high percentile.

The Panel estimated that daily consumption of an additional food supplement containing 0.35 g of potassium would for children aged 3-7 years, result in a total anticipated exposure of 2.45-3.35 g/day at the average level and a total anticipated exposure of 2.75-4.75 g/day at the high level.

Based on a potential intake of 0.35 g potassium/day in food supplements, as indicated by the petitioner, the equivalent intake of malic acid would be 1.5 g/day. No potential high intake groups of malic acid have been identified.

Table 3. **Summary information on potassium intake and anticipated exposure to malic acid from potassium malate**

Nutrient: Potassium	**Intake (g/day)**		**References**
Acceptable range of intake adult	3.1-3.5		EFSA, 2005b
Tolerable Upper Intake Level (UL)	No UL, no observed effects at 3 g/d in addition to diet		EFSA, 2005b
Nutrient: Potassium	**Average intake (g/day)**	**High intake (95^{th} or 97.5^{th}) (g/day)**	**References**
Intake range from food in Europe for adults	2.7-4.0	4.2-5.5	EFSA, 2005b
Intake range from food in Europe for children (3-17 years)	2.1-3.0	2.4-4.4	EFSA, 2005b
Amount of potassium added to supplements from potassium malate as indicated by petitioner (g/d)	0.35	0.35	Technical dossier, 2008
Source: Potassium malate			
Total anticipated exposure to potassium from supplement and food intake[1] for adults.	3.05-4.35	4.55-5.85	calculation by Panel
Total anticipated exposure to potassium from supplement and food intake[2] for children (3-17 years).	2.45-3.35	2.75-4.75	calculation by Panel

[1]calculation based on proposed use level of 0.35 g/day plus average dietary intake of 2.7-4.0 g/day and high dietary intake of 4.2-5.5 g/day for adults

[2]calculation based on proposed use level of 0.35 g/day plus average dietary intake of 2.1-3.0 g/day and high dietary intake of 2.4-4.4 g/day for children

3. Biological and toxicological data

3.1. Absorption, distribution, metabolism and excretion

No data on the bioavailability of magnesium and potassium from the different sources were provided by the petitioners. Magnesium succinate and magnesium pyruvate are highly soluble in water. Similarly, potassium malate is highly soluble in water and dissociates in the gastrointestinal tract. The Panel therefore assumed that magnesium and potassium are readily absorbed from these sources within the gastrointestinal tract.

Although calcium acetate is highly soluble in water, its succinate and pyruvate salts are only slightly to sparingly soluble in water. However, it has been shown that the solubility of a calcium source does not appear to correlate with its bioavailability from the human gastrointestinal tract (Heaney *et al.*, 1990). Instead, the absorption of calcium from the

gastrointestinal tract is primarily determined by food components, especially organic acids, and hence bioavailability is difficult to predict (Greenwald, 1938; Heaney *et al*., 1990).

The absorptions and metabolic fates of calcium, magnesium and potassium cations have been thoroughly described previously by the SCF and the European Food Safety Authority (EFSA) (SCF, 2001; SCF, 2003; EFSA, 2004; EFSA, 2005a; EFSA, 2005b; EFSA, 2006).

The absorption and metabolic fate of succinic, pyruvic, acetic and malic acid as intermediary metabolites of glucose in glycolysis and the Krebs cycle have been well described. The available evidence shows that D(+)-malate is metabolised without difficulty and there is no clear evidence for a need to distinguish between the enantiomers when malate is used in food (SCF, 1990). Recently, a cell surface receptor for succinic acid has been identified. The cognate receptor G protein-coupled receptor-91 (GPR91) in neurons has a major role in retinal angiogenesis, and extracellular succinate may be involved in revascularisation (Sapieha *et al.*, 2008).

3.2. Toxicological data

No specific toxicological data were provided by the petitioners neither on the succinate, pyruvate and acetate salts of calcium or magnesium, nor on the malate salt of potassium.

The Panel reviewed an acute oral toxicity study of calcium pyruvate; three Wistar rats of each sex dosed by oral gavage with 2000 mg/kg bw showed no mortality and no clinical or macroscopic signs of toxicity. Furthermore, *in vitro* genotoxicity tests using four *S. typhimurium* strains with up to 5 mg calcium pyruvate/plate were negative (Technical dossier, 2009).

Numerous human studies have investigated the effect of high level calcium pyruvate supplementation during physical training, on body fat and metabolic responses to exercise.

Early studies indicated that calcium pyruvate and sodium pyruvate supplementation enhances weight and fat loss and improves exercise capacity primarily in overweight individuals (Stanko *et al.,* 1992; Stanko *et al.,* 1994). Hence, pyruvate has recently become a popular weight-loss supplement and a performance enhancing aid. However, these findings remain unconfirmed and the consensus opinion is that calcium pyruvate supplementation during physical training does not significantly affect body composition or exercise performance (Ebersole *et al.,* 2000; Koh-Banerjee *et al.* 2005; Morrison *et al.,* 2000).

In a study, twenty-three untrained women were matched and assigned to ingest in a double blind and randomized manner either 5 g of calcium pyruvate or a placebo twice daily for 30 days while participating in a supervised exercise program (Koh-Banerjee *et al.,* 2005). The subjects who used calcium pyruvate showed an increase in fasting serum levels of very low-density lipoprotein cholesterol and triacylglycerol, whereas levels of high-density lipoprotein (HDL) cholesterol were significantly decreased. The 10 g of calcium pyruvate administered daily during this study is well above the levels recommended by the petitioner. However, two other studies on 40 and 34 hyperlipidaemic subjects, using daily doses of 13-25 g calcium pyruvate for 6 weeks in 40, showed no change in plasma HDL and triglyceride levels (Stanko *et al.,* 1992; 1994) and a 5% decrease (Stanko *et al.,* 1992) or no change (Stanko *et al.* 1994) in plasma cholesterol levels as compared to controls.

DL-malic acid as well as sodium malate , potassium malate and calcium malate are permitted food additives with the numbers E296, E350, E351 and E352i, respectively, and are therefore considered not to be of safety concern (EFSA, 2006). However, whilst the SCF agrees that DL-malic acid can be used for food supplements for adults, it considered only the L-isomer acceptable for use in foods prepared for infants and young children (SCF, 1992).

The toxicities of the cations magnesium, calcium and potassium has been evaluated by the SCF, UK Expert Group on Vitamins and Minerals (EVM) and EFSA (SCF, 2001; SCF, 2003; EVM, 2003). The succinate anion occurs in nature and plays a role as an intermediate metabolite in the Krebs cycle. It also participates in glucose and fatty acid synthesis. Although no systematic toxicological studies are available, it has been shown that consumption of succinic acid by rats results in a decreased weight increment of adult animals kept on an abundant sugar diet (Saakjan *et al.,* 1994). The results from a 1990 study on the toxicity/carcinogenicity of monosodium succinate had shown neither toxicity nor carcinogenic activity in F344 rats after continuous administration at levels of 1 or 2% in the drinking-water for 2 years (Maekawa *et al.,* 1990). From this study it appears that succinic acid has no carcinogenic properties.

The malate anion is a normal component of foods and plays a role as an intermediate metabolite in the Krebs cycle. No systematic toxicological studies are available. Foods containing malic acid have been consumed by man for centuries. The toxicity of malate has been evaluated by EFSA (EFSA, 2006) and JECFA (JECFA, 1969).

Pyruvate and acetate occur in nature. Pyruvate has a role as a final metabolite in glycolysis from where it can be converted to either acetyl CoA for further metabolism in the Krebs cycle or to lactate during anaerobic metabolism. Acetate is formed during ethanol metabolism and is a precursor in fatty acid synthesis. No systematic toxicological studies are available.

4. Discussion

Although no data were provided by the petitioners, human and animal studies indicate that magnesium and calcium are readily absorbed from orally ingested soluble organic salts. The Panel expects the bioavailability of calcium from the less soluble pyruvate and succinate salt sources to be comparable to that of readily soluble salts given that the absorption of calcium from the gastrointestinal tract is primarily determined by food components, especially organic acids. Similarly, potassium from potassium malate is readily absorbed from the gastrointestinal tract.

No data were provided by the petitioners on the metabolic fate of calcium, magnesium, potassium, succinate, pyruvate, acetate and malate. However, the Panel noted that succinate, pyruvate, acetate and malate are normal constituents of the body with well documented biochemical fates in the Krebs cycle or the glycolytic pathway.

No specific toxicological data were provided by the petitioners on the succinate, pyruvate and acetate salts of calcium or magnesium, nor on the malate salt of potassium. Studies in humans that have investigated the effect of calcium pyruvate supplementation during physical training on body fat and metabolic responses to exercise (with daily doses of 13-25 g calcium pyruvate for 6 weeks in hyperlipidaemic subjects) did not describe any adverse effects except for one study where adverse changes in serum lipid composition at 10 g daily were

documented. An acute oral toxicity study of calcium pyruvate in three Wistar rats of each sex dosed by oral gavage with 2000 mg/kg bw showed no mortality and no clinical or macroscopic signs of toxicity. Furthermore, *in vitro* genotoxicity tests on four *S. typhimurium* strains with up to 5 mg calcium pyruvate/plate were negative. DL-malic acid and potassium malate are permitted food additives with the numbers E296 and E351, respectively. JECFA evaluated malic acid, and derived on the basis of its well-established metabolic pathway and the daily consumption of malic acid-containing food by adults, a group ADI not specified for DL-malic acid and potassium DL-malate.

The toxicities of the cations magnesium, calcium and potassium have been evaluated by the SCF, the EVM and EFSA.

The petitioner, for calcium succinate and calcium pyruvate, proposed that the quantity of calcium to be added to food supplements as calcium succinate or calcium pyruvate will be up to 800 mg calcium/day. The petitioner for calcium acetate proposed its use as tablets containing 110 mg or 167 mg calcium; however, it is not clear from the dossier what the proposed daily exposure to calcium acetate would be. The Panel considered as for others calcium supplements (calcium succinate or calcium pyruvate) that the quantity of calcium to be added to food supplements as calcium acetate will also provide up to 800 mg calcium/day. In the case of the 97.5 percentile European dietary calcium intake population, the Panel noted that the total anticipated exposure to calcium for users of calcium succinate, calcium pyruvate or calcium acetate with the use levels proposed by the petitioners more food intake may exceed at the high percentile intake the UL of 2500 mg/day for calcium, established for adults by the SCF.

The UL for magnesium supplements defined by the SCF for adults is 250 mg/day. The petitioner states that the quantity of magnesium succinate or magnesium pyruvate 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, as defined by SCF.

No UL has been established for potassium but it was stated by EFSA's NDA Panel that long-term supplementary intake of up to 3 g/day, in addition to intake from foods, has been shown not to have an adverse effect in adults. The petitioner proposes that the quantity of potassium malate to be added to food supplements will supply up to 350 mg potassium/day.

No ULS have been defined by the SCF for succinate, pyruvate, acetate and malate. Based on an anticipated intake of 800 mg calcium/day in food supplements, as indicated by the petitioner, the maximum exposure to succinate, pyruvate and acetate from the respective sources as proposed by the petitioners would be 2, 3.4 and 2.4 g/day, respectively. The maximum exposure to malate from potassium malate would be 1.5 g/day. Combined intake of succinate and pyruvate salts from the proposed sources of calcium and magnesium would increase the exposure to these anions to 3.2 and 5.2 g/person/day, respectively. No adverse effects for the proposed quantities of succinate, acetate and malate have been reported. A daily exposure of up to 46 g pyruvate has been shown in two studies to have no adverse effects although one study reported an increase in fasting serum levels of very low density lipoproteins and triglycerides in subjects exposed to 10 g pyruvate/day.

CONCLUSIONS

The present opinion deals only with the safety of magnesium succinate, calcium succinate, magnesium pyruvate, calcium pyruvate, calcium acetate, and potassium malate added for nutritional purposes in food supplements and with the bioavailability of the nutrient cations from these sources. The safety of magnesium, calcium and potassium themselves, in terms of amounts that may be consumed, is outside the remit of this Panel.

The Panel noted that the proposed supplementation with calcium succinate, calcium pyruvate, calcium acetate, magnesium succinate and magnesium pyruvate, will not exceed the ULs for calcium and magnesium, established for adults in Europe. However, the total anticipated exposure to calcium with the use levels proposed by the petitioners may exceed the UL of 2500 mg/day for calcium at the high percentile dietary intake established for adults.

The Panel concludes the following:

- Calcium is expected to be bioavailable from the three sources of calcium (calcium succinate, calcium pyruvate and calcium acetate) to be used as nutritional substances in food supplements;
- Magnesium is expected to be bioavailable from the two sources of magnesium (magnesium succinate and magnesium pyruvate) to be used as nutritional substances in food supplements;
- Potassium is expected to be bioavailable from potassium malate which is to be used as a nutritional substance in food supplements;
- The use of calcium acetate, calcium succinate, calcium pyruvate, magnesium succinate, magnesium pyruvate and potassium malate, as sources of calcium, magnesium and potassium, in food supplements for the uses and at the use levels proposed by the petitioners is not of safety concern, provided that the UL for intake of the cations is not exceeded. However, the Panel notes that when the dietary intake is also taken into consideration, with supplementation of calcium succinate, calcium pyruvate or calcium acetate at the proposed daily use levels of up to 800 mg calcium, the UL defined by SCF for calcium would be exceeded for the 97.5 percentile European adult population;
- The intake of pyruvate, succinate, malate and acetate from the corresponding sources is not of safety concern.

DOCUMENTATION PROVIDED TO EFSA

1. Technical dossier, 2005a. Dossier on Magnesium Succinate 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 UK.
2. Technical dossier, 2005b. Dossier on Calcium Succinate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. May, 2005. Submitted by Health Food Manufacturers Association UK.
3. Technical dossier, 2005c. Dossier on Magnesium Pyruvate 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 UK.
4. Technical dossier, 2005d. Dossier on Calcium Pyruvate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. May, 2005. Submitted by Health Food Manufacturers Association UK.
5. Technical dossier, 2005e. Submission for use of calcium acetate in nutritional supplements. July, 2005. Submitted by Fresenius Medical Care Deutschland GmbH, Germany.
6. Technical dossier, 2008. Dossier on Potassium Malate Proposed for Addition to Annex II of Directive 2002/46/EC of the European Parliament and of the Council Relating to Food Supplements. February, 2008. Submitted by BioCare Ltd, UK.

ADDITIONAL INFORMATION PROVIDED TO EFSA

1. Technical dossier, 2009. Supporting information on Calcium Pyruvate. February 2009. Submitted by PhytoLab GmbH & KG. Germany.

REFERENCES

AFSSA (Agence française de sécurité sanitaire des aliments), 2009. AFSSA, report of the 2006/2007 individual and national study on food consumption 2 (INCA2, coordinator L. Lafay), February 2009. Available at: www.afssa.fr.

Antonelli ML, Spadaro C, Tomelli RF, 2008. A microcalorimetric sensor for food and cosmetic analyses: L-Malic acid determination. *Talanta* 74 (5), 1450-1454.

Ebersole KT, Stout JR, Eckerson JM, Housh TJ, Evetovich TK, Smith DB, 2000. The effect of pyruvate supplementation on critical power. *Journal of Strength and Conditioning Research* 14, 32-134.

EC (European Commission), 2008. Commission Regulation (EC) No 629/2008 of 2 July 2008 amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Union* L 173, 03.07.2008, p. 6.

EFSA (European Food Safety Authority), 2004. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium Sulphate as a mineral substance in foods intended for the general population. *The EFSA Journal* 112, 1-10.

EFSA(European Food Safety Authority), 2005a. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Magnesium Aspartate as a mineral substance when used as a source of magnesium in dietary foods for special medical purposes. *The EFSA Journal* 167, 1-6.

EFSA (European Food Safety Authority), 2005b. 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 Potassium. *The EFSA Journal* 193, 1-19.

EFSA (European Food Safety Authority), 2006. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium, Magnesium and Zinc Malate added for nutritional purposes to food supplements as sources for Calcium, Magnesium and Zinc and to Calcium Malate added for nutritional purposes to foods for particular nutritional uses and foods intended for the general population as source for Calcium. *The EFSA Journal* 391a,b,c,d, 1-6.

EFSA (European Food Safety Authority), 2007. Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium citrate malate as source for calcium for use in foods for Particular Nutritional Uses and in foods for the general population (including food supplements). *The EFSA Journal* 612, 1-2.

EVM (Expert Group on Vitamins and Minerals), 2003. Safe upper levels for vitamins and minerals, Food Standards Agency, London (2003). ISBN 1-904026-11-7.

Greenwald I, 1938. The dissociation of some calcium salts. *Journal of Biological Chemistry* 124, 437-452.

Heaney RP, Recker RR, Weaver CM, 1990. Absorbability of calcium sources: The limited role of solubility. *Calcified Tissue International* 46, 300-304.

JECFA, 1966. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. FAO Nutrition Meetings Report Series No. 40A,B,C. WHO/Food Add./67.29. Available at: http://www.inchem.org/documents/jecfa/jecmono/40abcj01.htm

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1969. Evaluations of D,L-malic acid. INS: 296. NMRS 46/TRS 445-JECFA 13/16

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1980. Evaluation of certain food additives (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 648.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1986. Evaluation of certain food additives and contaminants (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). *WHO Technical Report Series*, No. 733,

Koh-Banerjee PK, Ferreira MP, Greenwood M, Bowden RG, Cowan PN, Almada AL, Kreider RB, 2005. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. *Nutrition* 21, 312-319.

Maekawa A, Todate A, Onodera H, Matsushima Y, Nagaoka T, Shibutani M, Ogasawara H, Kodama Y, Hayashi Y, 1990. Lack of Toxicity Carcinogenicity of Monosodium Succinate in F344 Rats. *Food and Chemical Toxicology* 28, 235-241.

Morrison MA, Spriet LL, Dyck DJ ,2000. Pyruvate ingestion for 7 days does not improve aerobic performance in well-trained individuals. *Journal of Applied Physiology* 89, 549-556.

Saakjan MR, Kondrashova MN, Visochina IV, 1994. Correction of Internal Media in Animals and Man by Adding Succinic Acid with Food. *Izvestiya Akademii Nauk Seriya Biologicheskaya*, 596-604.

Sapieha P, Sirinyan M, Hamel D, Zaniolol K, Joyal JS, Cho JH, Honore JC, Kermorvant-Duchemin E, Varma DR, Tremblay S, Leduc M, Rihakova L, Hardy P, Klein WH, Mu XQ, Mamer O, Lachapelle P, Di Polo A, Beausiour C, Andelfinger G, Mitchell G, Sennlaub F, Chemtob S, 2008. The succinate receptor GPR91 in neurons has a major role in retinal angiogenesis. *Nature Medicine* 14, 1067-1076.

SCF (Scientific Committee for Food), 1990. First series of food additives of various technological functions (Opinion expressed on 18 May 1990).

SCF (Scientific Committee for Food), 1992. Minutes of the 86th meeting of the Scientific Committee for Food held on 8-9 October 1992.

SCF (Scientific Committee for Food), 1993. Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, Thirty First Series. European Commission, Luxembourg.

SCF (Scientific Committee for Food), 2001. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Magnesium. Expressed on 26 September 2001. SCF/CS/NUT/UPPLEV/54 Final. 11-10-2001.

SCF (Scientific Committee for Food), 2003. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Calcium. Expressed on 4 April 2003. SCF/CS/NUT/UPPLEV/64 Final. 23-4-2003.

Souci SW, Fachman W, Kraut H, 2008. Food composition and nutrition tables. Medpharm.

Stanko RT, Reynolds HR, Lonchar KD, Arch JE, 1992. Plasma-Lipid Concentrations in Hyperlipidemic Patients Consuming A High-Fat Diet Supplemented with Pyruvate for 6-Wk. *American Journal of Clinical Nutrition* 56, 950-954.

Stanko RT, Reynolds HR, Hoyson R, Janosky JE, Wolf R, 1994. Pyruvate Supplementation of A Low-Cholesterol, Low-Fat Diet -Effects on Plasma-Lipid Concentrations and Body-

Composition in Hyperlipidemic Patients. *American Journal of Clinical Nutrition* 59, 423-427.

Ysart G, Miller P, Crews H, Robb P, Baxter M, De L'Argy C, Lofthouse S, Sargent C, Harrison N. 1999. Dietary exposure estimates of 30 elements from the UK Total Diet Study. *Food Additives and Contaminants* 16, 391-403.

GLOSSARY / ABBREVIATIONS

AAS	Atomic Absorption Spectroscopy
ADI	Acceptable Daily Intake
AFC	Scientific Panel on Additives, Flavourings, Processing Aids and Materials in Contact with Food
AFSSA	Agence Française de Sécurité Sanitaire des Aliments
ANS	Scientific Panel on Additives and Nutrient Sources
BW	Body Weight
CAS	Chemical Abstracts Service
EC	European Commission
EFSA	European Food Safety Authority
GPR91	G Protein-coupled Receptor -91
HDL	High-Density Lipoprotein
ICP-AES	Inductively Coupled Plasma Atomic Emission Spectrophotometry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
NDA	Scientific Panel on Dietetic Products, Nutrition and Allergies
PARNUTS	Foods prepared for Particular Nutritional Uses
PRI	Population Reference Intake
SCF	Scientific Committee on Food
UL	Tolerable Upper Intake Level
WHO	World Health Organisation