European Food Safety Authority

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SCIENTIFIC OPINION

Benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride, as sources of vitamin B_1 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-2005-128, EFSA Q-2005-093, EFSA Q-2005-164, EFSA Q-2006-261)

Adopted on 24 September 2008

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission, the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion on sources of vitamin B_1 added for nutritional purposes to food supplements.

The present opinion deals only with the safety of benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride as particular sources of vitamin B_1, and with the bioavailability of vitamin B_1 from these sources, intended to be used in food supplements. The safety of vitamin B_1 itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

Thiamine monophosphate chloride and thiamine pyrophosphate chloride may be produced from 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 n° 1829/2003.

[1] For citation purposes: Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food (ANS) on a request from the Commission on benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride, as sources of vitamin B_1. *The EFSA Journal* (2008) 864, 1-31.

The European Population Reference Intake (PRI) set for vitamin B_1 for adult males and females is 1.2 and 0.9 mg/day, respectively. In most other countries recommended intake is between 1.0 and 1.4 mg/day for adult males and 0.8 and 1.1 mg/day for adult females.

Estimates based on food intake indicate that reported mean intake of vitamin B_1 in some European countries varied from 1.10 mg/day to 2.28 mg/day. In Europe high level intake (97.5^{th} percentile) varied from 1.90 to 6.35 mg/day. In the United States the median daily intake of thiamine from food is approximately 2 mg/day and the 95^{th} percentile of intake from both food and supplements was approximately 6.1 mg/day.

The Panel notes that these intakes from regular food seem to be adequate to reach the PRI.

A guidance level of a maximum of 100 mg/day of supplemental vitamin B_1 was defined by the EVM.

All petitioners indicate that intake recommendations for the sources will be consistent with the guidance level of 100 mg/day of supplemental vitamin B_1.

Thiamine monophosphate chloride and thiamine pyrophosphate chloride

The Panel concludes that the bioavailability of thiamine from thiamine monophosphate and thiamine pyrophosphate will be similar to that of thiamine.

There have been no toxicological studies carried out with thiamine monophosphate chloride and thiamine pyrophosphate chloride to evaluate reproductive and developmental toxicity, genotoxicity or long term toxicity of thiamine monophosphate chloride and thiamine pyrophosphate chloride.

However, given the facts that:

- thiamine monophosphate and thiamine pyrophosphate are endogenous metabolites of thiamine,
- these forms are interconvertible,
- thiamine monophosphate and thiamine pyrophosphate are naturally present in the diet,
- absorption of thiamine monophosphate and thiamine pyrophosphate is preceeded by their conversion to thiamine,
- the EVM defined a guidance level of 100 mg/day of supplemental vitamin B_1,

the Panel concludes that the use of thiamine monophosphate and thiamine pyrophosphate as a source of thiamine at the proposed levels of use in food supplements is not of safety concern, provided that the maximum of 100 mg/day of supplemental vitamin B_1 holds for the sum of all thiamine sources.

Benfotiamine

Benfotiamine is absorbed much better than water soluble thiamine salts. Maximum plasma levels of thiamine are about 5-fold higher after benfotiamine intake and the bioavailability is about 3.6 times as high as that of thiamine hydrochloride and better than that of other lipophilic thiamine derivatives. The increase in relative bioavailability is most significant in muscle (5-fold greater incorporation) and brain (25-fold increase), but thiamine from benfotiamine is also 10-40% better incorporated in other organs, such as liver and kidney. The

Panel concludes that the bioavailability of thiamine from benfotiamine is higher than that from other sources.

For benfotiamine several human clinical studies at dose levels from 40 up to 400 mg/day for several (3-12) weeks do not report adverse effects, except for one study conducting an open trial at a dose level of 40 mg benfotiamine (dosed together with 90 mg pyridoxine hydrochloride and 250 μg cyanocobalamin for 12 weeks) and reporting nausea, dizziness, stomach ache and weight gain at the twelfth week of the study in 8.4% of the patients.

Benfotiamine is converted to thiamine, but given the facts that:

- benfotiamine is not endogenous in humans,
- the bioavailability of thiamine from benfotiamine is higher than that of other sources of thiamine,
- benfotiamine in its dephosphorylated form is absorbed and bioavailable,
- no toxicological studies have been provided for benfotiamine to evaluate reproductive and developmental toxicity, genotoxicity or long term toxicity of benfotiamine, and
- the animal and clinical studies referred to, which were without adverse effects, were not designed to study possible adverse effects of benfotiamine,

the Panel concludes that the submitted data are insufficient to demonstrate the safety of the proposed use and use levels of benfotiamine.

Key words:

Food supplements, benfotiamine, thiamine monophosphate chloride, thiamine pyrophosphate chloride, cocarboxylase, vitamin B_1, CAS N^o 22457-89-2, CAS N^o 273724-21-3, CAS N^o 532-40-1, CAS N^o 154-87-0, CAS N^o 59-43-8.

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BACKGROUND

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 requests for the evaluation of benfotiamine, thiamine monophosphate chloride, and thiamine pyrophosphate chloride 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

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 benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride added for nutritional purposes to food supplements.

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group B on Food Additives and Nutrient Sources added to Food for the preparation of this opinion:

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[2] OJ L 183, 127.7.2002, p. 51.

ASSESSMENT

1. Introduction

The present opinion deals only with the safety of benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride as particular sources of vitamin B_1 and with the bioavailability of the vitamin B_1 from these resources, intended to be used in food supplements. The safety of vitamin B_1 itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

2. Technical data

2.1. Chemistry

Benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride are to be used as sources of vitamin B_1 (thiamine). To allow comparison of their chemical structures to vitamin B_1, Figure 1 presents the chemical structure of vitamin B_1 (thiamine) (CAS Registry Number 59-43-8).

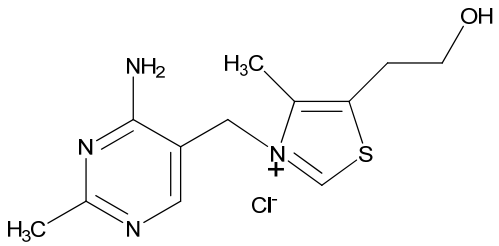

Figure 1. **Chemical structure of vitamin B_1 (thiamine)**

Thiamine can be esterified at the hydroxyethyl side chain. The most important esters are thiamine monophosphate, thiamine pyrophosphate and thiamine triphosphate (SCF, 2001). In most animal products 95-98% of thiamine occurs in a phosphorylated form, with about 80-85% as thiamine triphosphate. In plants thiamine occurs in the non-phosphorylated form (Gubler, 1991; Gregory, 1997).

Thiamine occurs in the human body as free thiamine and its phosphorylated forms: thiamine monophosphate, thiamine triphosphate, and thiamine pyrophosphate, of which the latter is also known as thiamine diphosphate or cocarboxylase.

Thiamine occurs in cells principally in its active coenzyme form called thiamine pyrophosphate (cocarboxylase). Thiamine, in the form of thiamine pyrophosphate, plays an essential role as a cofactor in key reactions in carbohydrate metabolism. It is also involved in the metabolism of branched-chain amino acids and may have non-coenzyme (non-cofactor) roles in excitable cells.

The total metabolic pool of thiamine in the body is approximately 30 mg. Approximately 80% of thiamine in blood is present in erythrocytes as thiamine pyrophosphate. About 50% of total body thiamine is present in skeletal muscles. Thiamine is also found in heart, liver, kidneys and brain. Other forms of thiamine present in the body include thiamine triphosphate (about

10%), thiamine monophosphate and free thiamine. Thiamine monophosphate and free thiamine comprise about 10% of total body thiamine.

Benfotiamine

Benfotiamine (synonym S-benzoylthiamine-O-monophosphate) is a so-called "allithiamine", a member of the class of lipophilic thiamine derivatives first identified in heated garlic in 1950 (Fujiwara *et al.,* 1954). It was later confirmed that similar compounds could be formed using other *Allium* vegetables from compounds similar to allicin, and a study in rabbits appeared to show that allithiamines are formed *in situ* in the intestine in the presence of garlic and thiamine (Fujiwara, 1976). Reaction with allicin and other sulphur compounds in *Allium* vegetables opens thiamine's thiazole ring, leading to a lipophilic molecule which, readily diffuses across cell membranes. The molecular formula of benfotiamine is $C_{19}H_{23}N_4O_6PS$, its molecular weight is 466.5 g/mol and its structural formula is presented in Figure 2. Its CAS Registry Number is 22457-89-2.

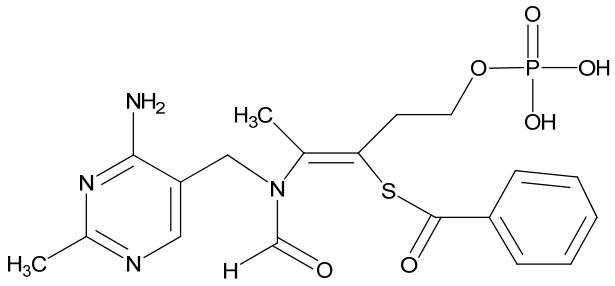

Figure 2. **Chemical structure of benfotiamine**

Thiamine monophosphate chloride

The chemical name of thiamine monophosphate chloride is 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl-4-methyl-5-[2-phopsphonooxy]ethyl]thiazolium chloride. Synonyms are thiamine monophosphate chloride, thiamine phosphoric acid ester chloride, phosphothiamine, monophosphothiamine, vitamin B_1 monophosphate, vitamin B_1 phosphate. The molecular formula proposed by the applicant corresponds with the dihydrate form ($C_{12}H_{18}ClN_4O_4PS.2H_2O$), its CAS Registry number is 273724-21-3 and its molecular weight is 416.8 g/mol. The CAS Registry Number for the anhydrous form is 532-40-1 and its molecular weight is 389.8 g/mol. The structural formula for the anhydrous form is given in Figure 3.

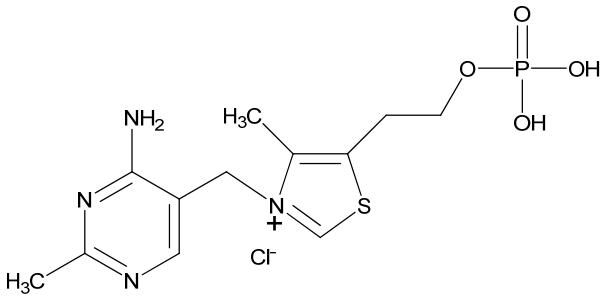

Figure 3. **Chemical structure of thiamine monophosphate chloride**

Thiamine pyrophosphate chloride

Thiamine pyrophosphate chloride is the diphosphate form of thiamine (vitamin B_1) and this form occurs in foods in vegetables, cereals, legumes, meats, yeast and *E. coli* (Golda *et al.,* 2004; Watanabe *et al.,* 2004; Machlin, 1984).

Thiamine pyrophosphate (cocarboxylase) is the enzymatically active form of vitamin B_1 (Machlin, 1984).

The chemical name of thiamine pyrophosphate chloride is 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-4-methyl-5-(4,6,6-trihydroxyl-3,5-dioxa-4,6-diphosphadex-1-yl)thiazolium chloride P,P'-dioxide. Its CAS number is 154-87-0.

Synonyms of thiamine pyrophosphate chloride are cocarboxylase (chloride), pyrophosphate of [(amino-4-methyl-2-pyrimidinyl-5)methyl-3-methyl-4-thiazolio-3-yl-5]-2-ethyl chloride, thiamin diphosphate chloride, TPP chloride, TDP chloride, thiamine diphosphate, thiaminium diphosphoric acid ester chloride, thiaminium pyrophosphate chloride, thiaminium pyrophosphoric acid ester chloride.

The molecular formula is $C_{12}H_{19}ClN_4O_7P_2S$, its molecular weight is 460.8, g/mol and its structural formula is given in Figure 4.

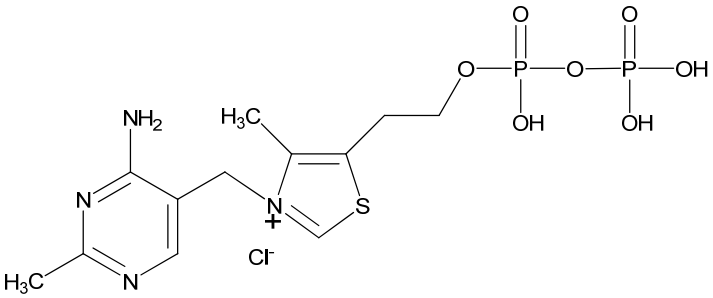

Figure 4. **Chemical structure of thiamine pyrophosphate chloride**

2.2. Specifications

Benfotiamine

Benfotiamine is a white crystalline powder slightly soluble in water and soluble in ethanol. The petitioner indicates that its purity is not less than 98.0% with the following limits for impurities: arsenic not more than 3 mg/kg, lead not more than 5 mg/kg, mercury not more than 1 mg/kg and heavy metals not more than 10 mg/kg. The loss on drying is not more than 1.5%.

Thiamine monophosphate chloride

Thiamine monophosphate chloride is a white to slightly yellowish, fine crystalline odourless powder. It is freely soluble in water, slightly soluble in methanol and practically insoluble in ethanol and chloroform. The pH of a 10% aqueous solution is 2.0-3.0.

The petitioner provided specifications indicating that the preparation contains not less than 97.0% thiamine phosphoric acid ester chloride on dry matter basis. Other constituents are thiamine dichloride (not more than 0.3%), chloride (9.0 - 9.6% calculated on the anhydrous substance), free phosphate (not more than 1%), heavy metals (not more than 20 mg/kg) and iron not more than 40 mg/kg. Loss on drying is 7.0-10%. The Panel notes that a significant proportion of the residual chloride results from thiamine monophosphate chloride itself.

Analysis of three representative lots of thiamine phosphoric ester chloride demonstrates compliance with the proposed specifications.

Thiamine pyrophosphate chloride

Thiamine pyrophosphate chloride is a white crystalline powder, colourless shiny plates or white crystals. It is soluble in water, freely soluble in glycerol (85%) and soluble in ethanol.

Both petitioners indicate that the purity of the preparations is not less than 93.0%.

One of the two petitioners indicates that loss on drying is <1.5%, and that other constituents are chloride 7.5-7.9%, sulphate not more than 100 mg/kg, arsenic not more than 3 mg/kg, lead not more than 5 mg/kg and heavy metals (as lead) not more than 10 mg/kg.

The other petitioner reports the following impurities: thiamine monophosphate not more than 4%, thiamine dichloride not more than 0.5 %, free phosphate not more than 1.0%, chloride 7.5-7.9%, sulphate not more than 0.01%, methanol not more than 2%, heavy metals as lead not more than 20 mg/kg and arsenic not more than 3 mg/kg. The Panel notes that a significant proportion of the residual chloride results from thiamine pyrophosphate chloride itself. This petitioner also indicates that endotoxins are less than 12 IU/gram. The petitioner indicates that methanol is a residual solvent obtained from the manufacturing process necessary to produce thiamine pyrophosphate chloride. Loss on drying is <1.5 and the pH of a 10% aqueous solution is 1.0-1.4.

2.3. Manufacturing Process

Benfotiamine

The petitioner indicates that benfotiamine is produced synthetically or is made by enzymatic synthesis using yeast phosphokinases. The petitioner also indicates that it may be derived from genetically modified micro-organisms. However this source is not part of the present opinion because it would require a separate submission under Regulation no 1829/2003.

Thiamine monophosphate chloride

Thiamine monophosphate chloride is obtained by chemical synthesis. Thiamine chloride is phosphorylated to the ester, which is subsequently acidified, precipitated in an organic solvent and isolated as the final product. The petitioner indicates that solvents, reagents and materials of the synthesis are commonly used in the production of ingredients for food use.

Thiamine pyrophosphate chloride

Thiamine pyrophosphate chloride is manufactured synthetically or is made by enzymatic synthesis using yeast phosphokinases. The petitioner indicates that it may be derived from genetically modified micro-organisms. However this source is not part of the present opinion because it would require a separate submission under Regulation no 1829/2003.

The second petitioner for thiamine chloride describes a manufacturing process under US patent 2992284 (Wenz *et al.*, 1961).

2.4. Methods of analysis in food

Benfotiamine

The petitioner indicates that benfotiamine can be analysed in food using high performance liquid chromatography (HPLC) with UV detection, following appropriate extraction.

Thiamine monophosphate chloride

The petitioner provided an analytical method to determine thiamine monophosphate in effervescent tablets. Thiamine monophosphate chloride can be quantified by high performance liquid chromatography (HPLC) with UV detection.

Thiamine pyrophosphate chloride

Thiamine pyrophosphate can be quantified by high performance liquid chromatography (HPLC) with UV detection. The method for extraction is dependent on the matrix.

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

Various interactions between food ingredients and thiamine have been described (EVM, 2002, 2003). Concomitant intake of thiamine and foods and beverages containing sulphites may inactivate thiamine. Concomitant intake of tea and coffee and thiamine may inactivate thiamine. Tannic acid is most likely the substance in tea that inactivates thiamine by forming a tannin-thiamine adduct. Coffee contains o-diphenols known to be dietary thiamine antagonists. Alcohol affects various aspects of thiamine transport/uptake, and these effects may contribute to the prevalence of thiamine deficiency in alcoholics. Alcohol also reduces cellular thiamine diphosphokinase activity. Certain seafoods contain thiaminase when raw. The EVM indicates that the significance of the effects of dietary thiaminase enzymes and thiamine antagonists on thiamine bioavailability has not been fully evaluated. The extent to which these interactions are relevant for benfotiamine, thiamine monophosphate and/or thiamine pyrophosphate has not been defined.

Benfotiamine

The petitioner states that benfotiamine is stable in foods but provided no data to support this claim.

Thiamine monophosphate chloride

Results of stability tests demonstrate that the chemical and physical properties of the crystalline substance are nearly identical after 36 months storage time, i.e. the substance is stable in the investigated packaging material at ambient temperature for at least 36 months.

The petitioner indicates that there are no indications of chemical interactions between thiamine monophosphate and components of the effervescent tablets in which the compound is to be used. Tablets containing 13 vitamins including thiamine monophosphate chloride, 12 minerals and appropriate food additives and flavours were stored either in aluminium tubes or in plastic tubes at 25°C (60% relative humidity), at 30°C (60% humidity) and at 40°C (75% relative humidity) for 6 months. Thiamine monophosphate chloride was found to be stable without decomposition for at least 6 months at all these conditions.

Thiamine pyrophosphate chloride

One of the two petitioners indicates that thiamine pyrophosphate chloride is relatively stable in foods in the absence of light and moisture and particularly in acid conditions.

The other petitioner for thiamine pyrophosphate chloride indicates that thiamine and thiamine pyrophosphate chloride are: i) increasingly unstable in solution at increasing pH, ii) decomposed by oxidizing or reducing agents and, iii) cleaved by sulphites very rapidly at high pH (DeRitter, 1982). Thiamine pyrophosphate degrades to thiamine monophosphate, thiamine and decomposition products produced by thiamine degradation.

The chemistry of degradation of thiamine and thiamine pyrophosphate under the influence of heat and pH has been described by Dwivedi and Arnold (1973) who reported that the oxidation pathway of both thiamine and thiamine pyrophosphate is a first order reaction with the rate increasing with the pH. The heating of thiamine solutions for 60 minutes at 75°C causes formation of sulphur, trichrome as well as 4-methyl-5-beta-(hydroxyethyl)thiazole. Thiamine destruction has been observed to occur completely within 24 hours in fluids containing bisulphite and having a pH greater than or equal to 6.0 (DeRitter, 1982). Thiamine

photochemical reduction has been reported (DeRitter, 1982) using UV radiation at 253.7 nm. The reactions take place at pH 3-9 with a rapid accelerated destruction at pH 4-5. At pH <3 the photolyzed thiazoles produce thiamine precipitates.

The petitioner also indicates that one of the major influences on stability of thiamine in food supplements is the presence of moisture and that the influence of iron and copper accelerates the decomposition of thiamine compounds such as thiamine pyrophosphate.

The stability of thiamine pyrophosphate in solution has been reported by Koval'chuk (1975) and occurs according to a first order reaction. Degradation products expected were thiamine monophosphate, thiamine and degradation products of thiamine. Although the first degradation product, thiamine monophosphate, still has vitamin B_1 activity, the final decomposition products would not support vitamin B_1 activity.

2.6. Case of need and proposed uses

Benfotiamine

Benfotiamine is to be used as a source of vitamin B_1 in food supplements including tablets, caplets, capsules, chewable tablets, effervescent powders and liquids. The petitioner indicates that the method of incorporation is determined by the individual manufacturers as appropriate for the particular type of finished product. The petitioner also indicates that intake recommendations for benfotiamine will be consistent with those described for vitamin B_1 salts and refers to the guidance level set by EVM of a maximum of 100 mg/day of supplemental vitamin B_1 (EVM, 2003).

Thiamine monophosphate chloride

Thiamine monophosphate chloride is intended to be used as a source of vitamin B_1 in food supplements. The petitioner indicates that thiamine monophosphate chloride shall be used in equimolar amounts with the same recommended daily dosages as two other vitamin B_1 sources, i.e. thiamine hydrochloride and thiamine mononitrate.

Thiamine pyrophosphate chloride

Thiamine-pyrophosphate chloride is to be used as an alternative source of vitamin B_1 as a nutrient in food supplements. It is intended for use in foods and dietary supplements as a stand-alone ingredient or in multi-ingredient formulas, as a powder, in tablets, 2 piece hard gelatine capsules or soft gelatine capsules. The petitioner indicates that intake recommendations for thiamine pyrophosphate will be consistent with those described for other vitamin B_1 salts.

The second petitioner for thiamine pyrophosphate chloride indicates that the compound is expected to be used in vitamin formulations such as tablets, capsules, powders or liquids which would be sold as food supplements. The petitioner also claims that technically thiamine pyrophosphate chloride may be preferred in some food supplement formulations based on taste, solubility and stability.

The quantities to be added to food supplements would be limited by the limits established for vitamin B_1 by the EVM (EVM, 2003). This petitioner indicates that it is expected that the daily dose of this vitamin would be between 0.2 mg/day and 100 mg/day.

2.7. Exposure

Vitamin B_1 (thiamine) is found in a large variety of animal and vegetable products. Good dietary sources of the vitamin include whole-grain products, brown rice, meat products, vegetables, fruits, legumes and seafood (EVM, 2003; SCF, 2001). Thiamine is synthesised by some micro-organisms, particularly yeasts.

According to the SCF (2001), the reported mean intake of vitamin B_1 in some European countries varied from 1.10 mg/day (Italy, German females) to 2.28 mg/day (Irish males) and the highest intake at 97.5th percentile from 1.90 (Italy) to 6.35 mg/day (Irish females). In the United States the median daily intake of thiamine from food is approximately 2 mg/day and the 95th percentile of intake from both food and supplements was approximately 6.1 mg/day (IOM, 1998).

Benfotiamine

The petitioner indicates that the anticipated exposure of the population to benfotiamine from food supplements is by self-selection of products containing multivitamins and multiminerals or as more specific combinations providing benfotiamine. Typical levels of benfotiamine included in food supplements amount to up to 100 mg/day at the recommended consumption.

Thiamine monophosphate chloride

Intake of thiamine monophosphate can result from its presence in animal food products. Other sources of thiamine monophosphate intake are medicinal products and food supplements which may contain 4.5 or 15 mg thiamine monophosphate per effervescent tablet. The petitioner indicates that thiamine monophosphate chloride will be used in equivalent doses. The petitioner also indicates that thiamine monophosphate chloride shall be used at the same recommended daily dosages as two other vitamin B_1 sources, i.e. thiamine hydrochloride and thiamine mononitrate.

Thiamine pyrophosphate chloride

The petitioner indicates that quantities to be added to food supplements will result in intake recommendations for thiamine pyrophosphate that are consistent with those described for other vitamin B_1 salts.

The other petitioner for thiamine pyrophosphate indicates that the quantities to be added to food supplements would be limited by the limits established for vitamin B_1 (EVM, 2002), and that it is expected that the daily dose of this vitamin would be between 0.2 mg per day and 100 mg per day.

2.8. Information on existing authorisations and evaluations

Thiamine has been evaluated for several authorisations in Europe and the USA. The European Population Reference Intake (PRI) for adult males and females is 1.2 and 0.9 mg/day, respectively (SCF, 2001). In most countries recommended intake is between 1.0 and 1.4 mg/day for adult males and 0.8 and 1.1 mg/day for adult females (EVM, 2002; D-A-CH, 2000; Health Council of the Netherlands, 2001; NNR, 2004).

The SCF concluded that due to the lack of systematic oral dose-response intake studies, as well as the extremely low toxicity, no LOAEL and NOAEL can be established (SCF, 2001). The SCF also concluded that "based on the presented evidence, it is not possible to derive a numerical UL for vitamin B_1. However, existing evidence that is available from clinical studies as well as the long history of therapeutic use indicates that current levels of intake from vitamin B_1 from all sources do not represent a health risk for the general population." The UK Expert Group on Vitamins and Minerals also concluded that there are insufficient data to establish a Safe Upper Level for thiamine. However, in the opinion of the EVM a level of 100 mg/day (equivalent to 1.7 mg/kg supplemental thiamine for a 60 kg adult) of supplemental thiamine would not be expected to result in adverse effects. This level is for guidance only and is applicable to the water-soluble forms of thiamine only. Also the US food and Nutrition Board concluded that they could not derive an UL because the data were inadequate (IOM, 1998).

Thiamine monophosphate was evaluated by the Therapeutic Goods Administration (TGA) of Australia / New Zealand as a new complementary medicine substance. At its meeting of 2 February 2001, the Complementary Medicines Evaluation Committee (CMEC) concluded that thiamine phosphoric acid ester chloride is safe for use in food supplements (CMEC, 2001). This conclusion was based on the following considerations:

- Thiamine monophosphate has a history of safe use both as a food additive and as an active ingredient in registered, non-prescription medicines
- Thiamine monophopshate was concluded to be bioavailable and metabolically interconvertible with free thiamine and thiamine pyrophosphate, the active form of thiamine
- Thiamine monophosphate is one of the phosphate esters of thiamine that is naturally present in the diet
- Thiamine nitrate and thiamine hydrochloride are already permitted as active ingredients in listable therapeutic goods, without any substance-specific restrictions on their use.

3. Biological and toxicological data

3.1. Bioavailability of vitamin B_1 (thiamine) from its various sources

Thiamine

The pharmacokinetics of benfotiamine (Loew, 1996) and of conventional thiamine salts (Loew, 1996; Rindi, 1996) have been reviewed. Thiamine is a charged molecule which does not readily diffuse at the gastrointestinal or cellular level. Thiamine is absorbed from the lumen of the small intestine, mainly the jejunum, by active transport and passive diffusion

mechanisms (PDR Health, 2005; Butterworth, 2003; Gregory, 1997; Said, 2004; Rindi and Laforenza, 2000; Gubler, 1991; Hoyumpa *et al*., 1982). At physiological concentrations (<1-2 μM) thiamine is primarily absorbed via active transport; at higher concentrations, passive diffusion is also significant. Absorption is usually limited to a maximal daily amount of 8 to 15 mg, but this amount can be exceeded by oral administration in divided doses with food (Gilman *et al.,* 1990). Others reporting on bioavailability of conventional thiamine salts state that doses above 2.5-5 mg are largely unabsorbed (Rindi, 1996). Cellular absorption is entirely dependent on an active transport mechanism, further limiting tissue uptake of the vitamin.

Data on the urinary excretion of thiamine after oral administration of a 50 mg bolus dose of thiamine hydrochloride indicate that the relative bioavailability is 5.3% (Tallaksen *et al*., 1993; Friedemann *et al*., 1948). A similarly low bioavailability is indicated by a comparison of the plasma thiamine concentration-time curves after oral and intravenous administration of doses of 50 - 200 mg thiamine (Weber and Kewitz, 1985).

After a normal meal, thiamine is mainly in the free form in the intestinal lumen, since its phosphoesters have probably been completely hydrolysed by different phosphatases of the gastrointestinal tract (Rindi and Laforenza, 2000)**.**

The cellular crossing is associated with intracellular enzymatic phosphorylation of thiamine to thiamine pyrophosphate. Subsequent enzymatic dephosphorylation yields thiamine monophosphate and thiamine. Additional amounts of thiamine monophosphate may be formed by transphosphorylation through the action of intestinal alkaline phosphatase (Rindi *et al*., 1995). Thiamine is metabolised to thiamine monophosphate, thiamine pyrophosphate (cocarboxylase), and thiamine triphosphate. Thiamine is phosphorylated directly to thiamine pyrophosphate by thiamine diphosphokinase, and thiamine pyrophosphate is dephosphorylated to thiamine monophosphate via thiamine diphosphatase. Approximately 80% of thiamine in blood is present in erythrocytes as thiamine pyrophosphate. The transport of thiamine into erythrocytes appears to occur by facilitated diffusion; it enters other cells by an active process. Total thiamine content in the adult body is about 30 milligrams.

Whereas thiamine pyrophosphate exists intracellularly exclusively, thiamine and thiamine monophosphate are present both intracellularly and extracellularly. In plasma, thiamine monophosphate is present at significant levels, although a specific physiological function of this metabolite is not known (Bettendorff *et al.*, 1986; Tallaksen *et al*., 1991, 1997). The thiamine monophosphate concentration exceeds that of thiamine in the cerebrospinal fluid (Rindi *et al*., 1981; Tallaksen *et al*., 1997). The uptake of circulating thiamine into most tissue cells appears to involve two specific transporters (Said, 2004). Uptake of circulating thiamine monophosphate, on the other hand, is mediated by the reduced folate carrier (Zhao *et al*., 2002). Once transported into the cells, thiamine monophosphate may be converted to thiamine by thiamine monophosphatase, followed by phosphorylation to thiamine pyrophosphate by thiamine pyrophosphokinase. Thiamine pyrophosphate is the physiologically active form of thiamine that acts as coenzyme in the decarboxylation of α-ketoacids and in transketolase reactions (Gubler, 1991). Thiamine taken up into the brain is phosphorylated to thiamine pyrophosphate by the enzyme thiamine pyrophosphokinase. Thiamine diphosphate is an essential cofactor for enzymes involved in brain glucose metabolism such as transketolase, pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (αKGDH). Thiamine pyrophosphate is then further phosphorylated to thiamine triphosphate or is dephosphorylated to thiamine monophosphate (Butterworth, 2003).

The distribution and storage of thiamine in organs and tissues, its catabolism and its excretion with the urine and bile has been the subject of several reviews (Gubler, 1991; McCormick, 1988; Tettamanti, 1985).

Thiamine and its metabolites are mainly excreted by the kidneys.

Benfotiamine

The pharmacokinetics of benfotiamine have been reviewed (Loew, 1996). The unique properties of the allithiamines result from the opening of thiamine's thiazole ring upon reaction with sulphur compounds in *Allium* vegetables. Upon dephosphorylation of benfotiamine in the intestinal tract (Rote Liste, 2008; Volvert *et al.,* 2008), a lipophilic molecule is produced which readily diffuses across cell membranes and is absorbed much better than water soluble thiamine salts. This property allows for greater absorption both in the intestines and in target tissues as compared with thiamine itself. Following uptake into the cell, the molecule undergoes catalytic reduction by intracellular sulphhydryl compounds and/or enzymatic debenzoylation (Rote Liste, 2008), closing the thiazole ring and releasing the active thiamin into the cell and circulation (Loew, 1996). Benzoic acid will be produced as a product from this debenzoylation (Rote Liste, 2008; Volvert *et al.,* 2008).

Maximum plasma levels of thiamine are about 5-fold higher after benfotiamine intake and the bioavailability is at maximum about 3.6 times as high as that of thiamine hydrochloride and better than that of other lipophilic thiamine derivatives. Human (Frank *et al.*, 2000; Greb and Bitsch, 1998; Bitsch *et al*., 1991, and studies reviewed in Loew, 1996) and animal (Geyer *et al.*, 2000; Hilbig and Rahmann, 1998; Karpov *et al*., 1986) studies confirm the much higher bioavailability and bioactivity of benfotiamine as compared with the standard water-soluble form of the vitamin. Benfotiamine leads to higher peak and integrated levels of thiamine and its phosphates in plasma, whole blood, red blood cells and tissues than does thiamine, and its plasma half-life is greater. The increase in relative bioavailability is most significant in muscle (5-fold greater incorporation) and brain (25-fold increase), but is also 10-40% better incorporated in other organs, such as liver and kidney (Hilbig and Rahman, 1998).

Increased tissue levels upon benfotiamine intake have also been reported in animal studies using radioactive labeled benfotiamine for especially brain, heart and diaphragma (Rote Liste, 2008).

A study by Volvert *et al.,* (2008) investigated whether intracellular thiamine and thiamine phosphate levels are increased in the brain of mice after a single oral benfotiamine administration of 100 mg/kg bw. They report that although thiamine levels rapidly increased in blood and liver no significant increase was observed in the brain. When mice received a daily oral administration of benfotiamine for 14 days, thiamine derivatives were increased significantly in the liver but not in the brain, compared to control mice. This is in contrast to the other studies reporting increased levels in brain. The authors also propose that benfotiamine only penetrates the cells after dephosphorylation by intestinal alkaline phosphatases, and that it enters the bloodstream as S-benzoylthiamine that is converted to thiamine in erythrocytes and the liver.

Thiamine monophosphate

Thiamine monophosphate has been studied *in vitro* in a membrane diffusion apparatus simulating gastrointestinal absorption. Optimum pH for absorption was found to be 3. Diffusion of thiamine monophosphate decreased as the pH increased (Correa *et al*., 1982).

Rat everted jejunal sacs were incubated for 15 and 30 min at 37 ^{o}C in oxygenated Krebs-Henseleit buffer, pH 7.4, containing 0.2 µM [^{3}H]-thiamine (^{3}H-T) or [^{3}H]-thiamine monophosphate (^{3}H-TMP). ^{3}H-TMP was transported partly unchanged by an active mechanism similarly to ^{3}H-T but less efficiently. During transport, ^{3}H-TMP was also enzymatically transformed to thiamine and thiamine pyrophosphate, which accumulated in the tissue. In the serosal fluid, the concentration of ^{3}H-TMP exceeded that of ^{3}H-T. Presence of L-phenylalanine or levamisole, two potential thiamine transport inhibitors, with ^{3}H-T or ^{3}H-TMP in the incubation medium reduced the serosal transport and the tissue content of thiamine compounds. The results indicated that the transport of thiamine monophosphate involves a number of different processes similar to those responsible for thiamine transport (Gastaldi *et al*., 1988).

A study in rats, suggests that thiamine present in beef, i.e. phosphorylated thiamine, is fully bioavailable (Day *et al*., 1957). A similar result was obtained in rat bioassays of yeast products, pork and various grain products, which also indicated nearly complete bioavailability (Harris and Wang, 1941). More recent evidence for the nutritional equivalence of thiamine (from plant derived foods) and thiamine phosphates (from animal derived foods) stems from a study in pigs, which were fitted with an end-to-end ileo-rectal anastomosis in order to eliminate an interference from thiamine synthesized by the intestinal flora. Using this model, the prececal digestibility of thiamine from different foods was determined. The prececal digestibility of thiamine from fish (73%), milk powder (88%) and boiled eggs (82%) was similar to that of rice, soybeans, barley (all 94%), white cabbage, corn (81%) and bananas (77%) (Roth-Maier *et al.*, 1999). It follows from these results that the phosphate esters of thiamine are about as bioavailable as thiamine itself.

Thiamine pyrophosphate chloride

The metabolic fate of thiamine was reviewed by the Expert Group on Vitamins and Minerals (EVM, 2002). The EVM stated that prior to absorption phosphorylated forms of thiamine undergo complete hydrolysis involving a number of intestinal phosphatases, and that consequently thiamine found in the intestinal lumen following a meal is in the free form (EVM, 2002; Haas, 1988).

Prececal digestibility of thiamine from various foods and feedstuffs was investigated in male pigs fitted with an end-to-end ileo-rectal anastomosis with preserved ileo-caeco-colicvalve (Roth-Maier *et al*., 1999). All the tested foods and feedstuffs, which would contain all forms of thiamine including thiamine pyrophosphate, exhibited a relatively good intestinal availability of thiamine.

Baker and Frank (1976) have reported the absorption of thiamine pyrophosphate. Oral administration of thiamine pyrophosphate was reported to increase thiamine levels in blood.

3.2. Toxicological data

The safety of thiamine (vitamin B_1) and its salts has been reviewed by several experts groups including the Expert Group on Vitamins and Minerals (EVM, 2002; 2003), the Scientific

Committee on Food (SCF, 2001; 2003) and the Hazardous Substances Databank (HSDB, 2002) and others (Guilland, 1995; Domke *et al*., 2005). The oral toxicity of thiamine and its derivatives in humans is considered very low (SCF, 2003).

This opinion will focus on specific safety information on benfotiamine, thiamine monophosphate and thiamine pyrophosphate.

3.2.1. Acute toxicity

Benfotiamine

No data available.

Thiamine monophosphate and thiamine pyrophosphate

The acute LD_{50} of thiamine monophosphate and thiamine pyrophosphate (cocarboxylase) was compared to the acute LD_{50} of thiamine by means of standard bioassay techniques (Causa and Perri, 1969). Three species, mouse, rat and rabbit, and two administration routes (IV and IP) were used. Thiamine monophosphate and thiamine pyrophosphate were found to be less toxic than thiamine. In addition, thiamine pyrophosphate appeared to be less toxic than thiamine monophosphate.

In an acute toxicity study in rabbits the minimum lethal dose of thiamine monophosphate was found to be about 5 times higher than that of thiamine (Genazzani and Reduzzi, 1954).

Similarly, a higher tolerance (but an identical bioefficacy) of parenterally administered thiamine monophosphate than of thiamine was observed in pigeons (Mouriquand *et al*., 1955a,b). A comparison of the LD_{50} of intravenously administered TPP and thiamine hydrochloride in the mouse and rat demonstrated that TPP has a lower acute toxicity than thiamine as well (Körner and Völlm, 1976).

3.2.2. Sub-acute and subchronic toxicity

Benfotiamine

No studies were provided designed to study the sub-acute or subchronic toxicity of benfotiamine. Animal studies in which high doses of up to 100 mg benfotiamine/kg bw for 6 months were administered, reported no adverse effects (Babaei-Jadidi *et al*., 2003; Hammes *et al*., 2003; Stracke *et al.,* 2001). The Panel notes that these studies were not designed to study the possible adverse effects of benfotiamine.

Thiamine monophosphate and thiamine pyrophosphate chloride

There have been no toxicology studies carried out with thiamine monophosphate or thiamine pyrophosphate to evaluate oral subacute or subchronic toxicity.

Comparison of the toxicity of thiamine, thiamine monophosphate and thiamine pyrophosphate was done by means of a prolonged administration experiment of 4 weeks in rats treated IP.

Thiamine monophosphate and thiamine pyrophosphate appeared to be less toxic than thiamine, when equimolecular doses of the 3 compounds were used. Equal molar IP doses of 240 mg thiamine equivalent/kg bw (50% of the LD_{50} for thiamine) were administered, to examine the subacute toxicity in the rat. After 28 days IP dosing the mortalities were 38% for thiamine, 15% for thiamine monophosphate and 0% for thiamine pyrophosphate. In addition, thiamine pyrophosphate was noted to be less toxic than thiamine monophosphate when doses of 50 % of the LD_{50} for the individual compounds were used (Causa and Perri, 1969).

3.2.3. Reproductive and developmental toxicity

There have been no toxicological studies carried out with benfotiamine, thiamine monophosphate or thiamine pyrophosphate to evaluate reproductive and developmental toxicity.

3.2.4. Genotoxicity

There have been no toxicological studies carried out with benfotiamine, thiamine monophosphate or thiamine pyrophosphate to evaluate genotoxicity.

3.2.5. Long term toxicity

There have been no long term toxicology studies carried out with benfotiamine, thiamine monophosphate or thiamine pyrophosphate.

3.2.6. Human studies

The EVM (2003) has given a thorough review of case reports and studies reviewing human toxicity of vitamin B_1.

Benfotiamine

The petitioner indicates that out of eleven trials with clinical endpoints, seven (Winkler *et al*., 1999; Woelk *et al*., 1998; Haupt *et al*., 1998; Barkai *et al*., 1998; Simeonov *et al*., 1997; Stracke *et al*., 1996; Ledermann and Wiedley, 1989) explicitly reported no side effects at all or no differences in side effect incidence between active and placebo groups.

The petitioner indicates that three trials, only available in abstract or poster format, provide less information, but also report no side effects (Lin *et al*., 2000; Sadekov *et al.,* 1998) or state that all the drugs tested were well tolerated (Kretschmar *et al*., 1996).

One study (Jermendy *et al.*, 1998) conducting an open trial with 141 patients at a dose level of 40 mg benfotiamine (dosed together with 90 mg pyridoxine hydrochloride and 250 µg cyanocobalamin for 12 weeks) reported nausea, dizziness, stomach ache and weight gain at the twelfth week of the study in 8.4% of the patients.

Barkai *et al*. (1998) reported a trial in 16 diabetic children administered 80 mg benfotiamine (along with 180 mg pyridoxine and 500 μg vitamin B_{12}) for twelve weeks and stated that side effects were not observed during the treatment period.

Most of the controlled trials (Winkler *et al*., 1999; Woelk *et a*l., 1998; Haupt *et al*., 1998; Simeonov *et al*., 1997; Stracke *et al*., 1996; Ledermann and Wiedley, 1989) also monitored a variety of biochemical parameters, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (gamma-GT), total and HDL cholesterol, triglycerides, creatine, alkaline phosphatase (ALP), white and red blood cell counts, hemoglobin, sodium, haematocrit, potassium, urea, uric acid, serum protein, and erythrocyte sedimentation rate, urine albumin, sugar and protein, as well as parameters most directly related to diabetic disease state. These trials have consistently shown that there were no statistically significant differences in these parameters between the exposed and control groups.

Die Rote Liste, the German formulary of pharmaceutical preparations approved for use in Germany, lists 5 different preparations including: i) dragees containing 50 mg of benfotiamine, ii) dragees containing 150 mg of benfotiamine, iii) capsules which contain 40 mg of benfotiamine and 90 mg pyridoxine HCl, iv) tablets which contain 100 mg each of benfotiamine and pyridoxine HCl, v) tablets containing 300 mg of benfotiamine and 100 mg of pyridoxine HCl (Rote Liste, 2007).

For the benfotiamine monotherapy products listed in the "Rote Liste, 2007" containing 50 mg or 150 mg benfotiamine (usual daily maximal doses: 150mg), the only contraindication given is “thiamine hypersensitivity" and the only side effects indicated are “in sole cases, hypersensitivity reactions (urticaria, exanthema)” (Rote Liste, 2007). Furthermore these products are assigned to the class of “Medicines for which after extensive application in humans, no suspicion of embryotoxic/teratogenic effects had resulted”. For the composite products (capsules with 40 mg of benfotiamine and 90 mg pyridoxine HCl, tablets with 100 mg each of benfotiamine and pyridoxine HCl, or tablets with 300 mg of benfotiamine and 100 mg of pyridoxine HCl) similar contraindication and side effects are indicated as for the monotherapy products, but including sole cases of anaphylactic shock.

Thiamine monophosphate chloride

No studies reported.

Thiamine pyrophosphate chloride

No studies reported.

4. Discussion

The present opinion deals only with the safety and bioavailability of benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride as particular sources of vitamin B_1, intended to be used in food supplements. The safety of vitamin B_1 itself, in terms of amounts that may be consumed, is outside the remit of this Panel.

The European Population Reference Intake (PRI) for adult males and females is 1.2 and 0.9 mg/day, respectively (SCF, 2001). In most countries recommended intake is between 1.0 and

1.4 mg/day for adult males and 0.8 and 1.1 mg/day for adult females (EVM, 2002; D-A-CH, 2000; Health Council of the Netherlands, 2001; NNR, 2004).

Estimates based on food intake indicate that reported mean intake of vitamin B_1 in some European countries varied from 1.10 mg/day to 2.28 mg/day. In Europe high level intake (97.5^{th} percentile) varied from 1.90 to 6.35 mg/day (SCF, 2001). In the United States the median daily intake of thiamine from food is approximately 2 mg/day and the 95^{th} percentile of intake from both food and supplements was approximately 6.1 mg/day (IOM, 1998).

The Panel notes that these intakes from regular food seem to be adequate to reach the PRI.

Absorption of thiamine salts is usually limited to a maximal daily amount of 8 to 15 mg, but this amount can be exceeded by oral administration in divided doses with food (Gilman *et al.*, 1990). Others reporting on the bioavailability of conventional thiamine salts state that doses above 2.5-5 mg remain largely unabsorbed (Rindi, 1996).

The petitioners want to add benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride as particular sources of vitamin B_1, for nutritional purposes to food supplements.

All petitioners indicate that intake recommendations for the sources will be consistent with the guidance level of 100 mg/day of supplemental vitamin B_1 set by EVM (EVM, 2003).

Thiamine monophosphate chloride and thiamine pyrophosphate chloride

Thiamine monophosphate and thiamine pyrophosphate (cocarboxylase) are naturally occurring forms of vitamin B_1 (thiamine) (Gubler, 1991; Gregory, 1997; Golda *et al*., 2004; Watanabe *et al*., 2004; Machlin, 1984). The oral absorption and bioavailability of thiamine monophosphate and thiamine pyrophosphate (cocarboxylase) in humans have been reported (Baker and Frank, 1976).

After a normal meal, thiamine is mainly in the free form in the intestinal lumen, since its phosphoesters have probably been completely hydrolysed by different phosphatases of the gastrointestinal tract (Rindi and Laforenza, 2000)**.** Therefore the Panel concludes that the bioavailability of thiamine from thiamine monophosphate and thiamine pyrophosphate will be similar to that of thiamine.

There have been no toxicological studies carried out with thiamine monophosphate chloride and thiamine pyrophosphate chloride to evaluate reproductive and developmental toxicity, genotoxicity or long term toxicity of thiamine monophosphate chloride and thiamine pyrophosphate chloride.

However, given the facts that:

- thiamine monophosphate and thiamine pyrophosphate are endogenous metabolites of thiamine,
- these forms are interconvertible,
- thiamine monophosphate and thiamine pyrophosphate are naturally present in the diet,
- absorption of thiamine monophosphate and thiamine pyrophosphate is preceeded by their conversion to thiamine, and
- the EVM defined a guidance level of 100 mg/day of supplemental vitamin B_1,

the Panel concludes that the use of thiamine monophosphate and thiamine pyrophosphate as a source of thiamine at the proposed levels of use in food supplements is not of safety concern provided that the maximum of 100 mg/day of supplemental vitamin B_1 holds for the sum of all thiamine sources.

Benfotiamine

Benfotiamine is absorbed much better than water soluble thiamine salts. Maximum plasma levels of thiamine are about 5-fold higher after benfotiamine intake and the bioavailability is about 3.6 times as high as that of thiamine hydrochloride and better than that of other lipophilic thiamine derivatives (Frank *et al*., 2000; Greb and Bitsch, 1998; Bitsch *et al*., 1991; studies reviewed in Loew, 1996; Geyer *et al*., 2000; Hilbig and Rahmann, 1998; Karpov *et al.,* 1986).

The increase in relative bioavailability is most significant in muscle (5-fold greater incorporation) and brain (25-fold increase), but thiamine from benfotiamine is also 10-40% better incorporated in other organs, such as liver and kidney (Hilbig and Rahman, 1998).

The Panel concludes that the bioavailability of thiamine from benfotiamine is higher than that from other sources.

The Panel notes that benzoic acid may be formed upon conversion of benfotiamine to thiamine. An amount of 100 mg benfotiamine will release 26.2 mg of benzoic acid. Given the ADI for benzoic acid of 5 mg/kg bw/day (JECFA, 1996), amounting to 300 mg benzoic acid for a 60 kg weight person, it can be concluded that the amount of benzoic acid that might be liberated from 100 mg of benfotiamine would not be of safety concern.

For benfotiamine, several human clinical studies at dose levels from 40 up to 400 mg/day for several (3-12) weeks do not report adverse effects, except for one study conducting an open trial at a dose level of 40 mg benfotiamine (dosed together with 90 mg pyridoxine hydrochloride and 250 μg cyanocobalamin for 12 weeks) and reporting nausea, dizziness, stomach ache and weight gain at the twelfth week of the study in 8.4% of the patients.

Benfotiamine is converted to thiamine, but given the facts that:

- benfotiamine is not endogenous in humans,
- the bioavailability of thiamine from benfotiamine is higher than that of other sources of thiamine,
- benfotiamine in its dephosphorylated form is absorbed and bioavailable,
- no toxicological studies have been provided for benfotiamine to evaluate reproductive and developmental toxicity, genotoxicity or long term toxicity of benfotiamine, and
- the animal and clinical studies referred to, which were without adverse effects, were not designed to study possible adverse effects of benfotiamine,

the Panel concludes that the submitted data are insufficient to demonstrate the safety of the proposed use and use levels of benfotiamine.

CONCLUSIONS

The present opinion deals only with the safety of benfotiamine, thiamine monophosphate chloride and thiamine pyrophosphate chloride as particular sources of vitamin B_1 and with the bioavailability of vitamin B_1 from these sources, intended to be used in food supplements. The safety of vitamin B_1 itself, in terms of amounts that may be consumed, is outside the remit of this Panel**.**

The Panel concludes that the bioavailability of thiamine from thiamine monophosphate and thiamine pyrophosphate will be similar to that of thiamine.

The Panel concludes that the use of thiamine monophosphate and thiamine pyrophosphate as a source of thiamine at the proposed levels of use in food supplements is not of safety concern, provided that the maximum of 100 mg/day of supplemental vitamin B_1 holds for the sum of all thiamine sources.

The Panel concludes that the bioavailability of thiamine from benfotiamine is higher than that from other sources. Benfotiamine in its dephosphorylated form is absorbed and bioavailable. Adequate toxicological studies to prove the safety of the source have not been provided.

The Panel concludes that the submitted data are insufficient to demonstrate the safety of the proposed use and use levels of benfotiamine.

DOCUMENTATION PROVIDED TO EFSA

1. Dossier on benfotiamine 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. Thiamine monophosphate (thiamine phosphoric acid ester chloride). Notification on behalf of Bayer Consumer Care Ltd. CH-4052 Basel Switzerland, of a lawfully marketed form of thiamine (vitamin B_1) pursuant to Article 4(6) of Directive 2002/46/EC on food supplements. April 14, 2005.
3. Dossier on Thiamine Pyrophosphate Chloride (cocarboxylase) 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.
4. Application for submission of a nutritional substance directive 2002/46/EC Article 4(6). June 6, 2005. Submitted by Biotics Research Corporations.

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GLOSSARY / ABBREVIATIONS

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANS	Scientific Panel on Food Additives and Nutrient Sources added to food
AST	Aspartate Aminotransferase
EVM	Expert Group on Vitamins and Minerals
gamma-GT	gamma- Glutamyltransferase
HDL	High Density Lipoprotein
IU	International Units
α-KGDH	α-Ketoglutarate Dehydrogenase
LOAEL	Lowest-Observed-Adverse-Effect Level
NOAEL	No-Observed-Adverse-Effect Level
PRI	Population Reference Intake
SCF	Scientific Committee for Food
UL	Upper Levels