

EXPERT GROUP ON VITAMINS AND MINERALS

REVISED REVIEW OF THIAMIN

The attached review of thiamin is a revised version of the paper first presented to the Expert Group on Vitamins and Minerals at the meeting on 21 July 2000. It has been amended to take account of some of the comments made by members and to correct a number of minor inaccuracies.

The following annexes are also included:

- Annex 1 Intakes of thiamin from food and supplements
- Annex 2 Tables 3, 4 and 5 referred to in the text
- Annex 3 Summary table of selected nutrition related information and existing guidance on regulations

Expert Group on Vitamins and Minerals Secretariat
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THIAMIN (VITAMIN B1)

Chemistry and nomenclature

1. Thiamin (CASRN: 59-43-8) is a water-soluble vitamin containing a pyrimidine and a thiazole nucleus linked by a methylene bridge. It has a slight characteristic thiazole odour and bitter taste.

structure of thiamin hydrochloride salt

Mol Wt: 300.84

pH of a 1% (w/v) aqueous solution = 3.13

pH of a 0.1% (w/v) aqueous solution = 3.58

Heat stable, potency not diminished at 100°C for 24 hrs

Destroyed rapidly at pH > 5.5

Anhydride product is hygroscopic in air

Synonyms and identifiers:

2. Thiamin
Vitamin B₁
Thiamin, chloride
Thiamin, monochloride
3-((4-amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride
Thiazolium, 3-((4-amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methyl chloride
Aneurin(e)

Phosphorylated forms include thiamin monophosphate (TMP), thiamin pyrophosphate (TPP – the physiologically active form) and thiamin triphosphate (TTP).

[Reference sources: HSDB (2000), Marcus and Coulston 1996]

Other (synthetic) forms:

3. Thiamin hydrochloride (Betaxin CASRN: 67-03-8)
Thiamin mononitrate

More lipid soluble forms include the disulphide and benzoyl forms e.g.

Thiamin disulphide (CASRN: 67-16-3)

Thiamin disulphide mono-orotate (thioratin)

Thiamin propyl disulphide

Sulbutiamine (isobutyryl-thiamin disulphide CASRN: 3286-46-2)
Fursultiamin (thiamin tetrahydrofurfuryl disulphide CASRN: 804-30-8, *approved in US circa 1996-7* (as stated by the HSDB, 2000)
Benfotiamin (CS-benzoyl thiamin-o-monophosphate (CASRN: 22457-89-2)
O, S-dibenzoyl thiamin hydrochloride

The lipid soluble forms of thiamin have not been considered in this review.

Occurrence in food, fortified foods, food supplements and licensed medicines

Food

4. Most of the natural thiamin content is lost in the production of white flour and polished rice and in the UK there is mandatory fortification of white and brown flour with thiamin to a level of not less than 0.24 mg/100g flour. Thus, cereal and cereal products are the main food source of thiamin, providing 38% of the total intake in young people aged 15-18 years (Gregory and Lowe 2000). Other foods rich in thiamin include meat products (particularly pork muscle), vegetables, milk and milk products, legumes, fruits and eggs (Rindi 1996 and references therein). Vegetables, potatoes and savoury snacks were found to contribute 26% and meat and meat products 21% of thiamin intake (Gregory and Lowe 2000, see Annex 1).

Fortified foods

5. In Australia, it was proposed by the National Health and Medical Research Council that selected alcoholic beverages and flour were to be fortified with thiamin as a preventative measure against alcoholic Wernicke's encephalopathy. A study by Connolly *et al* (1996) found that the cost per case of Wernicke's encephalopathy averted was least when beer was fortified and most when bread - making flour was fortified. However only the latter has been adopted. A previous study had found the cost of fortifying alcohol to be less than the cost of long term institutionalisation of alcoholics with the disorder (Centerwall *et al* 1978).

Supplements

6. The synthetic forms of thiamin used in most nutritional supplements (and food fortifications) are the mononitrate and the hydrochloride (Gregory 1997).

Licensed medicinal products for oral use

7. Forty-four medicinal products containing thiamin are authorised for sale in supermarkets and other retail outlets without the supervision of a pharmacist. The majority are multi-constituent products for the prevention or treatment of nutrient deficiencies. For prevention of deficiencies the doses recommended are generally 1-5 mg thiamin per day, whilst for treatment of deficiencies 10-35 mg per day is recommended. Three single nutrient products, specifically indicated for thiamin deficiency have recommended daily doses up to 300 mg. A further 35 products may only be sold in a

pharmacy. The indications and doses for these are generally similar to those for the general sales products.

Intakes and exposure

8. In the UK the average intake of thiamin from all sources for men and women was 2.01 mg and 1.61 mg, respectively (see Annex 1). Food supplements raised the average intake of thiamin by 18% for men and 30% for women. Thiamin intake, either excluding or including supplements, did not vary significantly with age.

9. Average thiamin intake of adult males in the US (1985 data) was 1.75 mg (0.68 mg/1000 kcal). Corresponding intakes for adult females and children aged 1-5 years were 1.05 mg (0.69 mg/1000 kcal) and 1.12 mg (0.79 mg/1000kcal), respectively (NRC 1989).

Recommended amounts

10. Body stores of thiamin are relatively low and a regular intake is required since large single doses are poorly absorbed. Requirement is related to energy consumption. UK reference values for thiamin (Department of Health 1991) are shown in Table 1. Epidemiological evidence indicates that beriberi (disease of thiamin deficiency) occurs when intake of thiamin is 0.2 mg/1000 kcal or less. However, other studies have established a minimum requirement of 0.4 mg/day (0.188 mg/1000 kcal) in sedentary elderly men for 2 years without any alteration in clinical state. The recommended dietary allowance consistent with good health is 0.5 mg/4200 kJ (1000 kcal) (NRC 1989). For an adult consuming ~2000 kcal/day, and assuming thiamin losses through cooking are ~20%, the recommended daily allowances are 1.4 and 1 mg for adult men and women, respectively. In pregnancy and lactation, thiamin intake should be increased to 1.6-1.8 mg/day (Rindi 1996 and references therein).

Table 1 Dietary Reference Values for Thiamin* (mg/1,000 kcal)

Age	Lower Reference Nutrient Intake	Estimated Average Requirement	Reference Nutrient Intake
0-3 months	0.2	0.23	0.3
4-6 months	0.2	0.23	0.3
7-9 months	0.2	0.23	0.3
10-12 months	0.2	0.23	0.3
1-3 years	0.23	0.3	0.4
4-6 years	0.23	0.3	0.4
7-10 years	0.23	0.3	0.4
Males			
11-14 years	0.23	0.3	0.4
15-18 years	0.23	0.3	0.4
19-50 years	0.23	0.3	0.4
50+ years	0.23	0.3	0.4
Females			
11-14 years	0.23	0.3	0.4
15-18 years	0.23	0.3	0.4
19-50 years	0.23	0.3	0.4
50+ years	0.23	0.3	0.4
Pregnancy	No increment		
Location:			
0-4 months	No increment		
4+ months	No increment		

*The LRNI and EARs for children over 1 year have been assumed to be the same as for adults, to parallel the RNI. RNI in mg/day based on EARs for energy are given in Table 1.

Table 1 (From Department of Health, 1991)

11. The mean thiamin content of human breast milk in the UK has been reported as 0.16 mg/l, which is ~ 0.23 mg/1000 kcal. The Infant Formula and Follow-on Formula Regulations (1995) specify a minimum thiamin content of 40 µg/100 kcal for infant formula (see Annex 3).

This paper has been prepared for consideration by the Expert Group on Vitamins and Minerals and does not necessarily represent the final views of the Group.

Analysis of tissue levels and thiamin status

12. Biochemical function tests for the assessment of thiamin status include the determination of erythrocyte transketolase activity (ETK), urinary thiamin excretion, before and after loading, and blood thiamin levels. ETK is determined by measuring the disappearance of pentose and appearance of hexose sugars in haemolysed red blood cells.

13. Activity is expressed as basal activity (ETKA –determined in an assay performed without the addition of TPP *in vitro*) or as the activation coefficient (ETK-AC – the difference between stimulated activity, determined in an assay performed with the addition of TPP *in vitro*, and basal activity, as a percentage of the basal activity). Thiamin deficiency is then associated with a decreased ETKA and an increased ETK-AC.

14. Urinary excretion of thiamin is an index of recent dietary intake. Urinary excretion in adults is usually > 66 µg/g creatinine, while values below 27 µg/g creatinine are indicative of deficiency. Changes are small at low physiological intakes and interpretation may be improved if 24-hour urine samples are taken. The “thiamin loading” test involves the measurement of thiamin excreted in urine in the 4 hours following a 5 mg dose. An excretion of <20 µg is indicative of deficiency.

15. Determination of thiamin levels in whole blood and erythrocytes requires sensitive HPLC assay methods (Rindi 1996 and references therein).

Table 2 (adapted from Finglas, 1993)

Biochemical tests for assessment of thiamin status

	Normal Range ¹	Marginal deficiency	severe deficiency
ETK-AC	1.00-1.15	1.15-1.25	>1.25
Erythrocyte TPP content (nmol/l)	>150	120-150	<120
urinary thiamin excretion (µg/24 hr)	>66	27-65	<27

¹Non-pregnant adults

16. Normal range and deficiency values for ETK-AC, erythrocyte TPP concentrations and urinary thiamin excretion are given in Table 2 (from Finglas 1993 and references therein).

Function

Coenzyme function

17. The major coenzymatic form of thiamin is thiamin pyrophosphate (TPP), which requires ATP, Mg²⁺, and thiaminpyrophosphokinase for its synthesis. TPP functions as coenzyme in the following enzymic reactions:

- (i) Non-oxidative decarboxylation of α -ketoacids – catalysed by pyruvate decarboxylase (mainly plants and yeast, first step in alcoholic fermentation)
 $\text{RCOCOOH} \rightarrow \text{RCHO} + \text{CO}_2$
- (ii) Oxidative decarboxylation – catalysed by the pyruvate, α -ketoglutarate (and other α -keto acids) and branched-chain amino acid (leucine, isoleucine and valine) dehydrogenase multienzyme complex systems. All these enzymes are intramitochondrial and produce acetyl-coenzyme A (CoA), succinyl CoA and the appropriate derivatives of branched chain amino acids, respectively, which are important in carbohydrate and lipid metabolism.
- (iii) Transketolation – catalysed by cytosolic transketolase. This is an important reaction in the pentose phosphate pathway, and allows the reversible conversion of three-, four-, five-, six- and seven- carbon sugars by the transfer of two- or three-carbon moieties. This pathway provides the major source of pentose sugars for the synthesis of nucleic acids and NADPH for fatty acid synthesis. (Rindi, 1996 and references therein).

Non-coenzyme function

18. Thiamin is a pharmacologic antagonist of acetylcholine, which may explain the nervous lesions caused by thiamin deficiency (Baugartner, 1991 and references therein).

19. A non-coenzymatic function for TPP has been proposed in nervous tissue. TPP is concentrated in neuronal cells and other excitable tissues such as skeletal muscle and is hydrolysed more rapidly during nerve stimulation. It has been shown to modulate chloride channels in rat brain and its content correlates with chloride permeability of brain membranes. TPP also activates maxi-Cl⁻ channels of neuroblastoma cells *in vitro* by controlling the number of functional channels, possibly by phosphorylation (Rindi, 1996 and references therein).

Deficiency

(Rindi 1996 and references therein).

20. The main cause of thiamin deficiency in developing countries is an inadequate dietary intake. However, in developed countries, deficiency is usually associated with chronic alcoholism.

21. The symptoms of sub-clinical thiamin deficiency, which may be fairly common in the developed world, include headache, tiredness, anorexia, tissue wasting and reduced productivity. Clinical deficiency in humans, and various animals, results in the disease known as beriberi, the major manifestations of which mainly affect the cardiovascular (wet beriberi) and nervous systems (dry beriberi).

22. Cardiovascular manifestations of beriberi include cardiac hypertrophy and dilatation, particularly of the right ventricle, tachycardia, respiratory stress and oedema of the legs. Neurological manifestations typically affect the lower extremities and include exaggerated tendon reflexes, polyneuritis and sometimes paralysis. In later stages of the disease, the upper extremities are also affected, resulting in muscle weakness and pain and convulsions. "Burning-feet" syndrome may also be a manifestation of thiamin deficiency, appearing early on in the course of polyneuropathy. In more severe cases, both cardiovascular and neurological symptoms may be present and the disease can be fatal.

23. In the human central nervous system, thiamin deficiency can lead to Wernicke encephalopathy and Korsakoff syndrome. The former is characterised by confusion, ataxia, ophthalmoplegia, psychosis, confabulation and coma. The latter is an amnesiac disorder, considered to be the psychotic component of the Wernicke disease. Both of these conditions are typical for alcoholics and manifest themselves as Wernicke-Korsakoff syndrome. Autopsy findings show mid- and lower- brain abnormalities. Administration of thiamin results in dramatic clinical improvement.

24. Encephalopathy associated with thiamin deficiency in rats is characterised by selective changes in the function of neurotransmitters. There is impairment of cholinergic neurotransmission and serotonin metabolism, particularly in the cerebellum, which, in rats, is the region of the brain associated with the highest thiamin turnover. Region-selective reductions in TPP-dependent enzymes have also been demonstrated. Loss of neurons in severe thiamin deficiency is likely to be due to impaired energy metabolism, focal acidosis, loss of transketolase activity and excitotoxic damage from regional increases in extracellular glutamate.

25. Alcoholics are deficient in thiamin as a consequence of low thiamin intake, impaired thiamin absorption and utilisation and possibly increased excretion. In addition, liver disease, which is frequent in alcoholics, exacerbates the situation.

26. Thiamin deficiency may also be responsible for fetal alcohol syndrome described in the offspring of alcoholic mothers and is characterised by growth retardation, psychomotor abnormalities and congenital malformations.

Deficiency in cancer patients

27. Thiamin deficiency is observed in several types of cancer and there have been reports in patients of deficiency-linked disturbances to the central nervous system, Wernicke-Korsakoff syndrome, severe lactic acidosis and beriberi. Deficiency is

probably the outcome of competition between the increased thiamin needs of the tumour and those of the host, resulting in hypovitaminosis within the host while tumour levels remain constant. Consequently, thiamin supplementation is considered essential in cancer patients and current cancer care protocols supply between 210-20,000% of the RDA (Boros *et al* 1998 and references therein).

28. Thiamin plays an important role as co-enzyme to transketolase (TK) in the synthesis of ribose as part of the non-oxidative pentose-phosphate pathway. The thiamin-dependent pathway has been shown to provide at least 85% of the ribose phosphate recovered from nucleic acids in tumour cells *in vitro* and, consequently, plays a central role in nucleic acid synthesis and therefore tumour cell proliferation. Furthermore, thiamin antagonists have been shown to inhibit the growth of tumour cells both *in vitro* and *in vivo* in experimental cancer models (Boros *et al* 1998 and references therein).

29. Thiamin deficiency in cancer patients is frequently observed during or following chemotherapy. It has been suggested that the development of chemotherapy resistant cells is accompanied by an increased thiamin need. There is also a suggestion that thiamin may interfere with chemotherapy although most of the evidence for this is from either *in vitro* studies or from experimental models of cancer. For example, it has been demonstrated that thiamin or its phosphorylated form, TPP, inhibits the cytotoxicity of methotrexate and blocks the antitumour effects of mechlorethamine in murine leukaemia cells and those of cyclophosphamide in Ehrlich's ascites tumours (Boros *et al* 1998 and references therein).

30. Consequently, suspicions have been raised that routine thiamin administration to cancer patients, in the absence of TK inhibitors, may be harmful. (Boros *et al* 1998 and references therein). However, as yet, there are no data from human trials to support this. Furthermore, although thiamin has been shown to be trophic in neuronal cell cultures, evidence that excess thiamin stimulates tumour cell proliferation has not been forthcoming.

Overview of reported beneficial effects

31. The only established therapeutic use of thiamin is in the treatment or prophylaxis of thiamin deficiency as may occur in pregnancy, lactation, diabetes mellitus, myoedema, various malabsorptive condition and chronic alcoholism. Commonly this is achieved by the administration of large intravenous doses (100 mg/l parenteral fluid). Once the deficiency is corrected, there is usually no need for further supplementation of the daily requirement, except in instances where gastric disturbance may preclude ingestion/absorption of adequate quantities of the vitamin (Marcus and Coulston, 1996 and references therein).

Treatment of primary (spasmodic) dysmenorrhoea

32. A randomised double-blind placebo-controlled study was carried out in 556 females (aged 12-21 years) from 14 schools and hostels in India, suffering from moderate

to severe spasmodic dysmenorrhoea. A daily oral dose of 100 mg of thiamin hydrochloride was given for 90 days followed by placebo for 60 days or vice versa. It was reported that, after the commencement of thiamin treatment, there was a complete cure in 87% of individuals and pain relief in a further 8% and that effects persisted for at least 2 months after the course of treatment was completed (Gokhale, 1996).

As a therapy in Alzheimer's disease

33. Evidence that thiamin supplementation may be an effective treatment in Alzheimer's disease is inconclusive. Although a number of studies have not indicated any beneficial effects to large supplemental doses of thiamin, the data have been described as "not wholly negative" (Bender 1999 and references therein). Nourhashemi *et al* (2000) have reviewed the role nutritional factors plays in protecting against Alzheimer's disease and referred to two studies (Tucker *et al* 1990, La Rue *et al* 1997) where cognitive skills in the elderly positively correlated with nutritional status with respect to several vitamins including thiamin. Nolan *et al* (1991) reported no beneficial effect of 3 g/day over a period of 12 months but Meador *et al* (1993), in a preliminary report that does not appear to have been followed up, claimed there was a mild beneficial effect of 3-8 g/day thiamin hydrochloride in patients treated for 1 month.

Effects on intensity exercise performance and recovery from exercise-induced fatigue

34. It has been suggested that high dose thiamin supplementation may be helpful in improving exercise performance (Nishiyama *et al* 1972, as cited by Webster *et al* 1997) and accelerating recovery from or preventing exercise-induced fatigue (Suzuki and Itokawa 1996). However, studies by Doyle *et al* (1997) and Webster *et al* (1997) have not shown any treatment-related improvement in high intensity exercise performance.

Improvement of ventricular function in patients with congestive heart disease receiving long-term furosemide therapy

35. Patients with congestive heart disease receiving long-term furosemide therapy have been found to be vitamin B₁ deficient and repletion of thiamin has been shown to result in an improvement in left ventricular function (Shimon *et al*, 1995 and references therein).

Treatment of leg cramps during pregnancy

36. Twenty-four out of twenty-five pregnant women supplemented with a combination of vitamins B₆ and B₁ were either completely or partially relieved of leg cramps (Avsar *et al*, 1996). There was no control group included in this study.

Interactions

Biochemical interactions

37. Thiamin acts as an acetylcholine antagonist

Interactions with drugs

38. Thiamin reportedly may enhance the effect of neuromuscular blocking agents (McEvoy 1994).

39. 5-Fluorouracil appears to be antagonistic to thiamin, possibly through competition for phosphorylation, which is required by each entity for its activation (Basu 1983 and references therein).

Interactions with alcohol

40. Alcohol affects various aspects of thiamin transport/uptake, and these effects may contribute to the prevalence of thiamin deficiency in alcoholics. Alcohol also reduces cellular thiamin diphosphokinase activity (McEvoy 1994).

Bioavailability

Methodology

41. The availability of absorbable thiamin from the diet has been determined by the assessment of pharmacodynamic response either in rat or human. A dose-response is obtained in rats using a protocol consisting of a depletion period of 10-14 days followed by a repletion period of 2-3 weeks, with growth rate as the biological end point and urinary, blood or liver thiamin or erythrocyte TK activity as the assessment of thiamin status. However, these assessments can be complicated by the effects of anorexia (which can result from thiamin deficiency) or from the effects of diet inpalatability.

42. Assessment of bioavailability generally involves the use of a controlled diet, administration of a test meal or dose and determining changes in the plasma/blood levels of the test substance with time. While this is appropriate for the assessment of high doses of thiamin, as found in supplements, at low doses, as occur in food, changes in plasma or whole blood thiamin are difficult to measure. However, relative bioavailability from food may be determined from urinary thiamin excretion that gives a linear response over a dose-range of 1-7.5 mg.

Availability of thiamin in food

43. Little is known regarding the availability of thiamin in specific foods. However, collectively, data suggest a high but incomplete availability of both naturally occurring and added forms of the vitamin in the diet (Gregory 1997 and references therein).

44. In rats, the availability of thiamin in green beans was found to be approximately equivalent to that in dried potato, whole-wheat flour and in control animal diet. Rat bioassays of beef, yeast products, pork, various grain products indicated complete or near complete availability. Studies in pigs have suggested that thiamin in potato was slightly more available than that in brown rice (Gregory 1997 and references therein). It was reported that only ~17% of the total thiamin in live preparations of Baker's Yeast was biologically available. However, this was an early study and the reliability of the thiamin assay could not be assessed (Gregory 1997 and references therein).

45. Assessments in rats showed that the availability of the endogenous thiamin in whole-wheat bread was 91% and 75%, based on erythrocyte TK and liver thiamin, respectively, relative to the response to thiamin mononitrate from thiamin restored white bread. The availability of thiamin from amaranth and drumstick leaves was found to be ~60% in human studies, on the basis of urinary thiamin relative to supplemental thiamin (Gregory 1997 and references therein).

46. Certain seafoods, e.g. clams, contain thiaminases when raw but not when cooked. Known dietary thiamin antagonists include several o-diphenols found in coffee. The significance of the effects of dietary thiaminase enzymes and thiamin antagonists on thiamin bioavailability has not been fully evaluated (Gregory 1997 and references therein).

General comments

47. Gregory (1997) commented that, on the basis of the existing literature, thiamin in most foods is either highly or totally available for absorption and utilisation by humans. Carefully controlled bioassays may accurately determine available thiamin, but the relevance of this data requires further assessment. Short-term protocols in thiamin saturated human subjects, based on plasma AUC or urinary excretion, may lack the necessary sensitivity for evaluating thiamin bioavailability from certain foods.

Bioavailability of supplements—water soluble derivatives

48. At high doses, the active uptake mechanism for thiamin is saturated and the process of slow passive diffusion predominates. As a consequence, the percentage absorbed of orally administered thiamin hydrochloride and other water soluble thiamins is very low and a single oral dose of 2.5-5 mg thiamin will appear to be largely unabsorbed (Levy and Hewitt 1971, Thompson and Levy 1972, Ventura *et al* 1969). Furthermore, daily absorption is usually limited to a maximum of 8-15 mg, although this may be increased by administration of divided doses with food. (Rindi, 1996 and references therein; Gregory 1997 and references therein; 1996 and references therein).

49. Thiamin hydrochloride and thiamin mononitrate are nutritionally equivalent for use as supplements and food fortification (although the mononitrate exhibits a greater stability in moist foods (Gregory 1997 and references therein).

Absorption, distribution, metabolism and excretion

Absorption of water soluble thiamin

50. The absorption of thiamin is dose-dependent. However, intestinal absorption of water soluble forms of thiamin occurs by two processes. At low μM concentrations, thiamin is absorbed mainly by a saturable Na^+ -dependent carrier-mediated transport system involving metabolic trapping through intracellular phosphorylation. At higher concentrations, absorption is by slow passive diffusion (Rindi 1996 and references therein, Gregory 1997 and references therein, Marcus and Coulston 1996 and references therein).

51. Consequently, at low physiological levels, the percentage of thiamin absorbed is very high. In contrast, the uptake of higher doses of thiamin follows saturation kinetics and the percentage absorbed is relatively small. Due to the slow rate of passive diffusion, the majority of a single oral dose of 2.5-5 mg thiamin will be largely unabsorbed.

52. Thiamin absorption is usually limited to a maximum of 8-15 mg/day, but this amount may be exceeded by oral administration in divided doses with food. (Rindi 1996 and references therein, Gregory 1997 and references therein).

53. Prior to absorption, phosphorylated forms of thiamin undergo complete hydrolysis involving a number of different intestinal phosphatases. Consequently, thiamin found in the intestinal lumen following a meal is in free form (Rindi 1996 and references therein, Gregory 1997 and references therein, Marcus and Coulston 1996 and references therein).

Absorption in diseased states

54. Anorexia, nausea and vomiting can result in reduced thiamin status by decreasing intake or reducing absorption (Gregory 1997 and references therein).

Impaired absorption in the elderly

55. Elderly persons may suffer from impaired absorption or utilisation. Studies in rats suggest that there may be an age-related decline in thiamin transport from the gut. However, this has not been fully evaluated in humans (Gregory 1997 and references therein).

Distribution and metabolism

56. Animal tissues contain thiamin in free form and in three phosphorylated forms (Figure 1). Thiamin pyrophosphate (TPP – the major active form) comprises ~80% of total, with thiamin triphosphate (TTP) making up 5-10% and thiamin and thiamin monophosphate (TMP) the remainder. The four forms are inter-convertible (see Figure 2).

57. Once absorbed, free thiamin and all phosphorylated forms are transported in erythrocytes. Plasma, on the other hand, contains only the free form and the monophosphorylated form, as does cerebrospinal fluid. Once distributed to the various tissues, thiamin is then phosphorylated to the pyrophosphate form (TPP). Total thiamin present in the adult human body is estimated to be in the region of ~ 30 mg and its biological half-life is ~ 9.5-18.5 days. Consequently, marginal deficiency can develop in a relatively short time. Concentrations of thiamin (found mainly in the form of TPP) vary between the different tissues with the highest being found in liver, followed by heart, the kidney, the skeletal muscle, then brain and lastly the small intestine. Tissue levels are generally lower in humans than in other mammals (Rindi 1996 and references therein; Gregory 1997 and references therein, Finglas 1993 and references therein).

58. In adults, ~ 1 mg of thiamin is degraded by the tissues (Marcus and Coulston, 1996 and references therein).

Figure 1

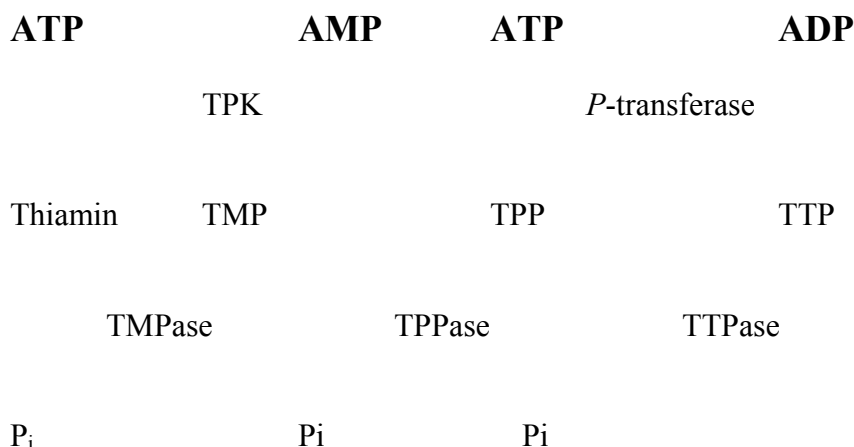
Thiamin and its phosphate esters

T	= thiamin (free base)
TMP	= thiamin monophosphate
TPP	= thiamin pyrophosphate (or diphosphate)
TTP	= thiamin triphosphate

Excretion

59. When intake of thiamin is low, little or no unchanged thiamin is excreted in the urine. However, absorbed thiamin that is in excess of tissue stores and coenzyme needs is rapidly cleared by the kidneys and excreted in the urine unchanged, free or phosphorylated, or as 20-30 different catabolites, including pyrimidine and thiazole moieties. As intake of thiamin is increased, the amount absorbed passively, although representing only a small percentage of the dose, and the amount of excess appearing as unchanged thiamin also increase (Rindi, 1996 and references therein; Gregory, 1997 and references therein; Marcus and Coulston, 1996 and references therein).

Figure 2 Enzymatic interconversion of thiamin compounds (adapted from Rindi, 1996)



TMP = thiamin monophosphate
 TPP = thiamin pyrophosphate
 TTP = thiamin triphosphate
 Pi = inorganic phosphate
 TPK = thiamin pyrophosphate kinase
 TMPase = thiamin monophosphatase
 TPPase = thiamin pyrophosphatase
 TTPase = thiamin triphosphatase

Toxicity

Oral toxicity in humans

60. Available data are summarised in Table 3 (see Annex 2).

61. It is generally accepted that ingested thiamin has a very low toxicity. However, this seems to be largely based upon anecdotal statements. Reviews and overviews of thiamin have widely failed to cite any formal supporting data. For example, Rindi (1996) stated that very high doses of thiamin have generally been found to be non-toxic in humans, with the exception of possible gastric upset. No supporting data were cited. Iber *et al* (1982) stated that toxic doses of thiamin were in excess of 50 mg/kg (>3 g/day). This seems to be based upon one or two case-reports but it is not clear how the threshold figure was derived. The UK Department of Health (1991) simply cite Iber *et al* (1982). The NRC (1989) state that there is no evidence of thiamin toxicity by the oral route and cite Hawk *et al* (1954). Hawk and colleagues, in turn, simply note, without further citation, “a remarkable tolerance to thiamin indicated by the fact that 500 mg have been taken daily for a month by normal people, without any objective symptoms”.

Case-reports of possible adverse effects associated with ingested thiamin

62. Mills (1941) reported thiamin-associated toxicity in a 47 year old woman from Cincinnati who had been taking 10 g thiamin hydrochloride daily for 2½ weeks (presumably by the oral route, although this is not totally clear from the article). This paper has been prepared for consideration by the Expert Group on Vitamins and Minerals and does not necessarily represent the final views of the Group.

Symptoms were reported to resemble those of over-dosage of thyroid extract – headache, increased irritability, insomnia, rapid pulse, weakness and trembling. Symptoms disappeared within 2 days following cessation of treatment but recurred 4¹/₂ weeks after the patient resumed a dose of 5 mg (*sic*)¹ /day. Again, prompt relief soon followed cessation of intake.

63. In the same report, Mills described symptoms similar to those of thyroid hyperactivity, with fine and coarse muscle tremor, rapid pulse and nervous hyperirritability in a young Panamanian woman receiving an average of 17 mg thiamin hydrochloride per day (again, this was presumed to be by the oral route but this was not made explicit). The woman was said to be excreting 12 mg/day in her urine and passing stools smelling strongly of thiamin. Mills stated that similar other cases had been reported to him.

64. The present author notes that the dose reported here as 17 mg is inconsistent with the quoted rate of urinary and likely fecal excretion and suggests that this is a text error within the Mills report that should read 17 g. Such an error would be consistent with an earlier error within the same report, indicated by Iber *et al* (see note¹ on previous page).

Thiamin intolerance, anaphylaxis, hypersensitivity and allergic effects

65. Thiamin intolerance has been reported following parenteral administration. Adverse effects have been described as asthma, urticaria, shock, severe allergic-like reactions including anaphylaxis, circulatory collapse and even sudden death (Hjorth 1958 and references therein). However, the occurrence is quite rare and parenteral doses of 100–500 mg are generally well tolerated (McEvoy 1994, as cited by HSDB 2000).

66. Generalised eczema was observed in a 17 year old woman working in the pharmaceutical industry filling vials with different vitamin preparations. The complaint disappeared when she ceased employment. A positive patch test for thiamin was observed. Flare ups reoccurred on occasions of resumed employment, experimental provocation by ingestion of 200 mg of thiamin and again following in cutaneous injection of 10 mg (Hjorth 1958).

67. As far as can be established, there have been just two case reports describing allergic type response or anaphylaxis secondary to oral administration of thiamin.

68. A 55 year old woman took 100 mg thiamin (aneurine) hydrochloride per day for 15 days with no reaction. Two months later she ingested a further single dose of 100 mg and was hospitalised within 24 hrs with acute skin rash, pruritis, chest pain, dyspnea and choking. Despite treatment with noradrenaline, hydrocortisone and adrenaline, the woman died the next day. Autopsy revealed pulmonary oedema and skin lesions only (Acharya *et al* 1969).

¹ The Mills report states 5 mg/day. However, when citing the Mills data, Iber *et al* (1982) state 5 g/day.

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69. It was suggested that oral administration (dose and form not stated) of thiamin could account for allergic encephalitis in a 25 year old man. A severe skin rash accompanied this reaction. Allergologic investigations showed a positive skin reaction to vitamin B₁ (Markiweicz and Uss 1970 – article in Polish, with abstract available in English, no further detail given).

Supplementation studies

70. Seventeen Alzheimer's patients (9M, 8F), mean age 69 years, were treated with thiamin hydrochloride 3 or 4 g/day, increasing in 0.5 g increments to 6 g/day for 3 months, followed by 1 month on placebo dose, followed by 1 month on 3-6 g/day. Seven patients continued to receive a similarly graduated dose, up to 8 g/day, over the next 5-6 months. Subjects were reported to have tolerated the doses well, without weakness or other side effects, with the exception of two subjects, who developed nausea and indigestion at dose levels of 7 and 7.5 g/day. These individuals were subsequently returned to their own previously highest tolerated doses (6.5 and 7.0 g/day) without side effects (Meador *et al* 1993).

71. In a study designed to investigate the effect of supplementation on relief from leg cramps, 25 pregnant women (5 in the second and 20 in the third trimester) were given a combination of pyridoxine (250 mg) and thiamin (250 mg, form not stated), orally, twice daily for 4 weeks. All pregnancies were normal and all babies were delivered healthy. There was no report of any adverse effects to the mothers (Avsar *et al* 1996).

72. Congestive heart failure patients on long-term furosemide treatment were treated with 200 mg/day thiamin hydrochloride *i.v.* or placebo injection (n = 15/group, mean ages 67 and 72 years, respectively) for 1 week and thereafter all patients received 200 mg thiamin hydrochloride /day orally for 6 weeks. One patient, who had received thiamin *i.v.* with no ill effect, developed nausea and insomnia during the first week of oral thiamin therapy. Nausea stopped when the oral thiamin dose was halved (Shimon *et al* 1995).

73. A group of 556 young women, suffering from primary (spasmodic) dysmenorrhoea, were treated with thiamin hydrochloride at a dose of 100 mg/day x 90 days. There was no report of any adverse effects (Gokhale 1996).

Potential vulnerable groups

Infants

74. Davis *et al* (1982) reported that post-mortem serum thiamin levels in infants dying from sudden infant death syndrome (SIDS) were generally higher than those from infants dying from other explicable causes (mean 144.3 µg/l, range 22 to >500, n = 233, compared to 26.5 µg/l, range <1 – 95, n = 46). Only 13% of SIDS infants had thiamin levels < 50 µg/l whereas 8.7 % of control infants had levels > 50 µg/l. The authors suggested that in infants dying from SIDS, the vitamin maybe freely absorbed leading to high blood levels. The authors also noted that death through SIDS had been associated

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with CNS depression and respiratory failure and, in experiments in mice, 2 - 3.5 mg thiamin by *i.v.* administration had caused death by depression of the respiratory centre (Haley and Flesher 1946, Haley 1948, Smith *et al* 1947).

75. However, there have been no further data in the literature to substantiate that high blood thiamin levels are either causally or casually associated with SIDS. Furthermore, Wyatt *et al* (1984) found non-physiological elevations of thiamin in almost all post-mortem blood samples regardless of their source and suggested that high thiamin blood levels were a post-mortem artefact.

Genetic variations

76. There are no known genetic variations resulting in increased susceptibility to thiamin toxicity. However, there are several inherited diseases associated with congenital defects in thiamin-associated metabolism.

Maple syrup urine disease (branched-chain disease)

77. Individuals with this disease lack the α -ketoacid dehydrogenase enzyme complex and are unable to degrade α -ketoacids by oxidative decarboxylation. Consequently, the urine and plasma contain high levels of α -ketoacids and branched-chain amino acids and the urine smells of maple syrup. The disease affects neonates and it is partially responsive to thiamin at high doses.

Lactic acidosis

78. Congenital lactic acidosis is a group of defects, related to faults in the pyruvate dehydrogenase complex. The disease is mainly observed in children and is characterised by lactic and pyruvic acidosis, neurological abnormalities and delayed development. Patients with lactic acidemia respond to high doses of thiamin.

Leigh disease

79. Leigh disease (sub-acute necrotising encephalomyelopathy) is a fatal disease that develops in infancy and early childhood and is associated with weakness, anorexia, difficulties with speech and eye motion, and cessation of growth. The disease is familial and possibly autorecessive. Neuropathological findings and clinical symptoms are similar to Wernicke's encephalopathy. Treatment with high doses of thiamin, preferably the lipophilic form, has been reported to be successful.

Thiamin-responsive megaloblastic anaemia

80. This is a rare disease of infancy and childhood, characterised by megaloblastic anaemia associated with sensorineural deafness and diabetes mellitus. Cardiac abnormalities and optic atrophy may also be present. Patients respond to thiamin therapy, but hearing deficit is only partially recoverable. The disease is associated with

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thiamin deficiency secondary to a reduced thiamin cellular transport and absorption, due to the absence of a membrane carrier and intracellular pyrophosphorylation. (Rindi 1996 and references therein).

Putative genetic variant of transketolase

81. There are considerable geographical differences in the prevalence of Wernicke-Korsakoff syndrome, which cannot be attributed to variations in alcohol consumption. Some data suggest that the syndrome may be associated with a genetic variant of transketolase that requires a higher than normal concentration of thiamin diphosphate for activity. This would imply the existence of a sub-population of individuals who have a higher than average thiamin requirement. However, the evidence is not convincing. Furthermore, it has been shown that multiple electrophoretically-separable forms of transketolase are not the result of variant alleles, tissue specific enzymes or differential splicing of mRNA but more likely due to differences in assembly of the holo functional enzyme or post-synthetic modification of the protein. (Bender *et al* 1999 and references therein)

Chronic toxicity/carcinogenicity

82. There is no evidence from the available data or the structure which indicates that thiamin or any of the previously mentioned thiamin derivatives is carcinogenic in humans. However, no direct data are available. It has been hypothesised that excess thiamin could result in the promotion of tumour growth (Boros *et al* 1998, see paragraphs 28-30). However, there are no human data to support this.

Oral toxicity in animals

83. There have been few studies reported in the literature concerning the toxicity of thiamin in animals by oral administration. Most indicate that the oral toxicity of thiamin is very low. The data from available studies are summarised in Tables 4 & 5 (Annex 2).

Acute and sub-chronic toxicity

84. A US FDA review on generally recognised as safe (GRAS) food ingredients, cited by Iber *et al* (1982) suggested that the oral LD50 for thiamin in rodents is ~ 3 g/kg. Shock, muscle tremor, convulsions and respiratory disturbances preceded death.

85. Molitor (1942) reported the oral LD50 for thiamin in mouse was 100 mg, which in an animal weighing ~20 g would be equivalent to 5 g/kg.

Thiamin nitrate

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86. As a preliminary test to determine a maximum tolerated dose for an investigation into the antinociceptive properties of thiamin, no toxic effects were observed in female NMRI mice (21-28 g) when administered thiamin nitrate in 0.8% aqueous hydroxypropyl methylcellulose gel at doses up to 5000 mg/kg *p.o.* (Leuschner 1992). The number of animals tested was not stated.

Developmental toxicity (teratogenicity)

87. There are no reports of thiamin supplement-associated teratogenic effects or adverse effects on development. In contrast, there are some animal data that suggest thiamin may be protective in the development of certain malformations.

88. A US FDA review on generally recognised as safe (GRAS) food ingredients, cited by Iber *et al* (1982), suggested that in rodents, thiamin up to doses of 50 mg/kg/day do not affect fertility, litter size or cause increased foetal malformations.

Thiamin hydrochloride

89. Groups (n = 12) of female weanling rats (strain not specified) were maintained on diets containing excess thiamin (7500 µg per 100g or 75 ppm [~ 4-8 mg/kg/day, present author's conversion]) or a control basal diet containing 150 µg thiamin hydrochloride per 100 g or 1.5 ppm. Animals were mated after 12 weeks. Addition of excess thiamin to the diet had no detrimental effects on the weight gain or reproductive performance in dams or survival or weight of offspring. Mothers that received excess thiamin actually produced more young than controls (Morrison and Sarett 1959).

Mutagenicity and genotoxicity

90. Thiamin hydrochloride was found not to be mutagenic in the Ames test (*S. typhimurium* strains TA97A and TA102), at doses of 0.1 - 10 mg/plate, both with and without metabolic activation (Fujita and Sasaki 1986, as summarised by HSDB 2000).

91. Thiamin hydrochloride was negative in both the Ames test at the maximum non-cytotoxic doses of 50, 5, 10, and 0.3 mg/plate, respectively and *in vitro* chromosomal aberration test at maximum non-cytotoxic concentrations of 0.04, 0.175, 0.25 and 8 mg/ml, respectively (Ishidate *et al* 1984).

92. Methanol-chloroform extracts of pyrolysates of thiamin hydrochloride prepared at temperatures of 300 - 600°C for 5 min were found to be mutagenic in *Salmonella typhimurium* strains TA98 and TA100 but only in the presence of a metabolic activating system (Demura *et al* 1990).

Adverse drug reactions

93. Suspected adverse drug reactions to medicinal products are reported to the Committee on Safety of Medicines/medicines Control Agency. Many factors influence

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the number of reports received, and in most situations there is considerable “under-reporting”. For products containing thiamin alone there were very few reports (4) of adverse reactions following oral administration, with no common factors. For multi-nutrient products the number of reactions reported was greater, but in the presence of the other constituents makes interpretation difficult.

Mechanisms of toxicity

94. None identified.

Regulatory considerations

95. The Infant Formula and Follow-on Formula Regulations specify a minimum thiamin level of 40 µg/100 kcal in infant formula. In cereal based infant foods the thiamin content should not be less than 100 µg/100 kcal. The Foods Intended for use in energy restricted diets for weight reduction Regulations (1997) specify that a whole daily diet replacement should provide 1.1 mg thiamin a day and a meal replacement 0.33 mg. The Bread and Flour regulations (1998) specify a thiamin content per 100 g white or brown flour of not less than 0.24 mg. The Recommended Daily Allowance used for food labelling purposes for thiamin is 1.4 mg (see Annex 3).

Guidance on high intakes

96. Based on the publication of Iber *et al* (1982) (see comments made in paragraph 66), COMA (Department of Health 1991) concluded that chronic intakes in excess of 50 mg/kg or more than 3 g/day are toxic to adults with a wide variety of clinical signs including headache, irritability, insomnia, rapid pulse, weakness, contact dermatitis, pruritus and in one case death.

Recommendations on maximum supplementation levels

97. The European Federation of Health Product Manufacturers Associations (EHPM) established an upper safe level of 50 mg thiamin but could not establish an upper limit for short term consumption (EHPM 1997).

Summary

98. Thiamin (vitamin B₁) is a relatively heat- and acid-stable, water-soluble compound, containing a pyrimidine and a thiazole nucleus linked by a methylene bridge. Derivatives of thiamin include the mono-, pyro- and tri-phosphate forms and the synthetic hydrochloride and the slightly less water-soluble mononitrate salt.

99. Foods providing rich sources of thiamin include unrefined grain products, meat products, vegetables, dairy products, legumes, fruits and eggs. In some countries refined products such as polished rice and white flour are often fortified with thiamin. Dietary

supplements available in the UK largely contain the mononitrate or hydrochloride derivatives of thiamin.

100. Body stores of thiamin are limited and a regular intake is necessary. Requirement is related to energy consumption. The Reference Nutrient Intake (RNI) for adults and children ≥ 1 year is 0.4 mg/1000 kcal and 0.3 mg/1000 kcal in infants. In adults, this is equivalent to ~ 1.4 and 1 mg/day in males and females, respectively. In pregnancy and lactation, thiamin requirement increases to $\sim 1.6 - 1.8$ mg/day.

101. Status may be assessed by determination of thiamin levels in blood or urine, before and after loading. Functional assessment can be assessed by measurement of erythrocyte transketolase (ETK) activity.

102. Thiamin in food appears to be highly available for absorption. However, although the absorption of thiamin hydrochloride and other water-soluble thiamins is dose-dependent, the absorption of high doses is relatively poor due to saturation of the rate limited transport mechanism. Relative to the water-soluble forms, the barely water-soluble forms, such as the disulphides, allithiamins and benzoyl thiamin derivatives, are not subject to rate limited transport and are highly bioavailable even at high doses.

103. Absorption of thiamin is dose-dependent. At physiological concentrations, intestinal uptake occurs mainly via a carrier-mediated transport mechanism. However, this process is saturable and at higher concentrations, uptake is predominately by slower passive diffusion.

104. In the blood and tissues, thiamin is present as the free form and mono-, di- (pyro) and tri-phosphorylated forms, which are interconvertible. Free and phosphorylated forms are transported within the erythrocytes but plasma and cerebrospinal fluid contain only the free and monophosphorylated forms. Within the tissues, most thiamin present is converted to the pyrophosphate form. Of all the tissues, liver contains the highest thiamin concentration. Total degradation in all tissues amounts to ~ 1 mg/day, and most of this occurs in the liver. Catabolised thiamin products and thiamin that is excess to requirement are excreted in the urine. The level of unchanged thiamin present in the urine increases as intake increases.

105. Thiamin pyrophosphate (TPP) acts as a coenzyme in reactions involving the pyruvate, α -ketoglutarate and branch-chained amino acid dehydrogenase multienzyme complexes, important in carbohydrate and lipid metabolism, and in transketolase catalysed reactions of the pentose phosphate pathway, important for the synthesis of NADPH and sugar moieties required for nucleic acid synthesis. TPP may also have a non-coenzyme function in neuronal cells during nerve stimulation.

106. The biological half-life of thiamin is $\sim 10 - 20$ days and marginal deficiency can develop quite rapidly. Symptoms of sub-clinical deficiency include headache, tiredness, anorexia and wasting. A regular daily intake of ≤ 0.2 mg/1000 kcal results in clinical thiamin deficiency and the disease known as beriberi, which affects the cardiovascular

and nervous systems. Thiamin deficiency can result in a disorder of the central nervous system known as Wernicke encephalopathy. This condition sometimes also has a psychotic component known as Korsakoff syndrome. Both conditions are typical for alcoholics and manifest themselves as Wernicke-Korsakoff syndrome.

107. In developed countries, most thiamin deficiency is associated with chronic alcoholism where intake of the vitamin may be low and its absorption and utilisation may be impaired.

108. Established therapeutic uses of thiamin supplements are largely related to treatment or prophylaxis of deficiency.

109. Reports of thiamin-associated toxicity in humans are rare and almost exclusively relate to incidents following parenteral administration of the vitamin. The oral toxicity of thiamin and thiamin derivatives in humans is generally considered very low. High doses (> 7 g) of thiamin hydrochloride may cause headache, nausea, irritability, insomnia, rapid pulse and weakness but these symptoms are relieved following cessation of treatment or reduction of dose. There have been a very small number of reported adverse effects following lower doses. These comprise four case reports and one isolated individual taking part in a supplementation study. Three of the case-reports concerned women, one who experienced muscle tremor, rapid pulse and nervous hyperirritability after taking daily doses of thiamin hydrochloride, reported to be 17 mg/day, another who, some 2 months after repeatedly taking 100 mg/day thiamin for a period of 15 days, suffered anaphylaxis and subsequently died following a single oral dose of 100 mg and one who suffered from thiamin-related contact dermatitis and experienced eczema flare up following experimental provocation with an oral dose of 200 mg. The fourth case-report involved a young man who contracted allergic encephalitis associated with an oral dose of thiamin (amount and form not clear). In the supplementation study, one isolated individual, who had earlier received parenteral exposure to thiamin hydrochloride, experienced nausea and insomnia following a daily dose of 200 mg/day thiamin hydrochloride for less than a week. Symptoms resolved when the dosage was halved. There is no evidence to suggest that thiamin or thiamin derivatives are carcinogenic or teratogenic in humans.

110. The animal toxicity database is limited. The oral LD₅₀ for thiamin/thiamin hydrochloride in rats and mice is in the order of 3 - 5 g/kg. Thiamin nitrate may be even less acutely toxic, with no adverse effects reported in mice following a single oral dose of 5 g/kg. The oral LD₅₀ for thiamin disulphide monoorthoate has been reported as 7.4 g/kg. There is an absence of chronic and sub-chronic data for high-dose exposure to the water-soluble thiamin derivatives.

111. There is no evidence to suggest that thiamin or thiamin derivatives are carcinogenic or teratogenic in animals.

112. Thiamin hydrochloride has been shown to be non-mutagenic in a range of bacterial mutagenicity and *in vitro* chromosomal aberration tests. However, methanol-

chloroform extracts of pyrolysates prepared from thiamin hydrochloride have been shown to be mutagenic in the Ames test in the presence of a metabolic activation system.

113. COMA (Department of Health 1991) concluded that chronic intakes in excess of 50 mg/kg or more than 3 g/day are toxic to adults with a wide variety of clinical signs including headache, irritability, insomnia, rapid pulse, weakness, contact dermatitis, pruritus and in one case death. The European Federation of Health Product Manufacturers Associations (EHPM) established an upper safe level of 50 mg thiamin but could not establish an upper limit for short term consumption (EHPM 1997).

Glossary

AUC	area under the concentration curve
bw	body weight
CYP	cytochrome P450
DH	Department of Health
EAR	estimated average requirement
ETK	erythrocyte transketolase
ETKA	basal erythrocyte transketolase activity
FDA	Food and Drug Administration (US)
HPLC	high performance liquid chromatography
ETK-AC	erythrocyte transketolase activation coefficient
GRAS	generally recognised as safe (US)
HSDB	Hazardous Substances Data Bank (US)
LD50	Lethal dose (causing death to 50%)
LNRI	Lower reference nutrient intake
NRC	National Research Council (US)
ppm	parts per million
SIDS	sudden infant death syndrome
RNI	Reference Nutrient Intake
TK	transketolase
TMP	thiamin monophosphate
TPP	thiamin pyrophosphate
TTP	thiamin triphosphate
TTFD	thiamin tetrahydrofurfuryl disulphide

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ANNEX 1 TO EVM/00/14.REVISED SEPT2001

INTAKES OF THIAMIN FROM FOOD AND SUPPLEMENTS

The data presented on thiamin intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years^{2,3,4,5,6}. In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of manufactured foods over time.

Total intakes of thiamin

Table 1 provides information on the absolute intakes of thiamin by the British population, classified by age and sex. Mean and median intake, and the upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), are given. In addition, intakes of thiamin from food and supplements for older people are presented both including and excluding prescribed thiamin supplements, for comparison. Although these prescribed preparations were only taken by a small minority of participants within this group, intakes from them were found to have a disproportionate impact on mean daily intakes of thiamin.

Average intakes of thiamin from food were lowest for pre-school children, and highest for males aged 11 to 64 years. Mean intakes from food sources increased significantly with age for boys aged 4-18 and for girls aged 4-14 years but not for older girls, pre-school children or adults. Mean intakes from food sources decreased significantly with age for older people free-living in the community.

Mean and median thiamin intakes (from food sources and from all sources, including prescribed supplements) were above the Reference Nutrient Intakes for each group. Intakes from food and supplements (including prescribed thiamin supplements) at the 97.5%ile were about 2-3½ times the median in all groups (except infants where data regarding intakes of thiamin supplements is unavailable).

Table 2 provides information on thiamin intakes from food and supplements adjusted for body weight classified by age and sex. This shows a trend to decrease with age particularly in the 4 to 18 year group. Bodyweight adjusted thiamin intakes are highest in

² Food and nutrient intakes of British infants. 1986

³ National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

⁴ National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8

⁵ Dietary and nutritional survey of British adults. 1986/7

⁶ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

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infants. This is in part due to the high consumption of fortified infant formulas and commercial infant foods.

Sources of thiamin in the diet

Table 3 indicates the contribution made by different types of food to average intakes of thiamin by young people aged 15-18 years. This dataset was collected in 1997 and so most closely reflects current eating habits and fortification practices.

The main food source of thiamin in this age group is cereal and cereal products (38%), of which about half came from breakfast cereals, followed by vegetables, potatoes and savoury snacks (26%), then meat and meat products (21%).

For adults and older people, cereals and cereal products followed by vegetables, potatoes and savoury snacks, are also the main sources of thiamin. The main source of thiamin for infants is commercial infant foods. They obtain a third of their thiamin intake from this source.

UK legislation requires that not less than 0.24mg thiamin per 100g flour be added as a fortificant to all wheat flour except wholemeal flour. Thiamin is often also added voluntarily by manufacturers to other foods such as breakfast cereals, some soft drinks and some savoury snacks.

Thiamin intakes from supplements

For pre-school children, dietary supplements containing thiamin contributed very little to population average intakes of this nutrient. For young people, and older people living in institutions, dietary supplements provided around 1-2% of population average intakes of thiamin. For adults aged 16 to 64 years supplements provided about 20% of population average intakes of thiamin, and around a quarter for older females aged 35 to 64 years. For older people aged 65 years and over free-living in the community, supplements provided 20% of population average intakes, and 61% for females aged 65 to 74 years, dropping to 42% when prescribed supplements containing thiamin are excluded from the dataset. Of course, the proportion of intake from supplements is much higher if supplement consumers are considered separately.

Table 4 (see Annex 1) shows the number of consumers of dietary supplements containing thiamin in each age group, together with the mean, median and range of intakes of thiamin from supplements for those who consumed them. The prevalence of thiamin supplement use ranged from about 1-8% across all groups.

The highest intakes of thiamin from supplements by those who consumed them are for adults and older people free-living in the community. The high intakes of thiamin from supplements in the older people was due in part to the use of high strength thiamin tablets, some of which were prescribed, B complex multivitamin tablets, multivitamin and mineral supplements and yeast based supplements. It should be borne in mind that

the data for adults aged 16-64 years was collected in 1986/87 and use of supplements may have changed since then.

Diet and Nutrition Surveys Branch
Nutrition Division
Food Standards Agency
July 2000

Table 1: Total intakes of thiamin

Age/sex	Absolute thiamin intake (mg/day) ⁷							
	Food Only				Food and Supplements			
	2.5% ile	Mean	Median	97.5 % ile	2.5% ile	Mean	Median	97.5% ile
Infants (1986) 6-12mths M&F	0.5	1.1	1.0	2.0	*	*	*	*
Pre-school children (1992/3)								
1½-2½ yrs/M&F	0.4	0.7	0.7	1.3	0.4	0.8	0.7	1.6
2½-3½ yrs/M&F	0.4	0.8	0.7	1.5	0.4	0.8	0.8	1.7
3½-4½ yrs/M	0.4	0.9	0.9	1.4	0.4	0.9	0.9	1.7
3½-4½ yrs/F	0.4	0.8	0.8	1.3	0.4	0.9	0.8	1.8
Young people (1997/8)								
4-6 yrs/M	0.51	1.27	1.22	2.60	0.51	1.28	1.23	2.60
4-6 yrs/F	0.56	1.14	1.05	2.33	0.57	1.17	1.07	2.38
7-10 yrs/M	0.77	1.42	1.37	2.29	0.77	1.43	1.37	2.38
7-10 yrs/F	0.70	1.27	1.23	2.17	0.70	1.29	1.23	2.31
11-14 yrs/M	0.72	1.70	1.54	2.97	0.72	1.71	1.55	2.97
11-14 yrs/F	0.68	1.40	1.29	2.45	0.68	1.42	1.30	2.51
15-18 yrs/M	0.84	1.90	1.81	3.70	0.84	1.93	1.83	3.86
15-18 yrs/F	0.53	1.38	1.21	2.78	0.53	1.41	1.24	2.77
Adults (1986/7)								
16-24 yrs/M	0.72	1.72	1.68	2.85	0.76	1.93	1.72	3.92
16-24 yrs/F	0.52	1.26	1.23	2.30	0.54	1.46	1.26	2.42
25-34 yrs/M	0.85	1.66	1.57	2.96	0.90	2.28	1.62	3.13
25-34 yrs/F	0.55	1.21	1.18	2.02	0.55	1.32	1.21	2.73
35-49 yrs/M	0.79	1.71	1.65	2.85	0.79	1.95	1.65	3.25
35-49 yrs/F	0.57	1.25	1.24	1.98	0.58	1.56	1.29	3.18
50-64 yrs/M	0.78	1.70	1.69	2.83	0.78	1.87	1.69	3.13
50-64 yrs/F	0.70	1.25	1.23	2.05	0.70	2.05	1.27	4.49
Older people free-living in the community (1994/5)								
65-74yrs/M	0.76	1.53	1.50	2.43	0.81 (0.79)	1.70 (1.60)	1.53 (1.51)	3.20 (2.99)
65-74yrs/F	0.55	1.22	1.22	1.92	0.56 (0.56)	3.09 (2.11)	1.26 (1.25)	2.35 (2.31)
75-84 yrs/M	0.63	1.43	1.37	2.48	0.63 (0.63)	1.54 (1.50)	1.39 (1.39)	2.84 (2.80)
75-84 yrs/F	0.48	1.16	1.12	1.97	0.51 (0.51)	1.29 (1.28)	1.13 (1.13)	2.97 (2.64)
85 & over/M	0.56	1.39	1.34	2.58	0.57 (0.56)	1.52 (1.46)	1.41 (1.40)	3.23 (3.00)
85 & over/F	0.48	1.10	1.07	1.85	0.47 (0.48)	1.21 (1.14)	1.10 (1.09)	2.62 (2.14)
Older people living in institutions (1994/5)								
65-84 yrs/M	0.58	1.35	1.31	2.25	0.58 (0.58)	1.35 (1.35)	1.30 (1.32)	2.24 (2.25)
65-84 yrs/F	0.55	1.21	1.10	1.91	0.58 (0.58)	1.22 (1.22)	1.10 (1.10)	1.90 (1.91)
85 & over/M	0.71	1.34	1.31	2.29	0.65 (0.71)	1.41 (1.34)	1.32 (1.31)	2.51 (2.29)
85 & over/F	0.55	1.07	1.07	1.70	0.57 (0.55)	1.11 (1.11)	1.07 (1.08)	1.97 (1.86)

*Data unavailable

⁷ Data in brackets = intakes from food and supplements, excluding prescribed thiamin supplements.

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Table 2: Bodyweight adjusted thiamin intake

Age/sex	Bodyweight adjusted thiamin intake (mg/kg bwt /day) ⁸		
	<i>intakes from food and supplements⁹</i>		
	Mean	Median	97.5% ile
Infants (1986)¹⁰ 6-12mths/M&F	0.12	0.11	0.22
Pre-school children (1992/3) 1½-2½ yrs/M&F	0.06	0.06	0.13
2½-3½ yrs/M&F	0.06	0.05	0.11
3½-4½ yrs/M	0.05	0.05	0.10
3½-4½ yrs/F	0.05	0.05	0.10
Young people (1997/8) 4-6 yrs/M	0.06	0.06	0.11
4-6 yrs/F	0.06	0.05	0.11
7-10 yrs/M	0.05	0.05	0.09
7-10 yrs/F	0.04	0.04	0.08
11-14 yrs/M	0.04	0.03	0.07
11-14 yrs/F	0.03	0.03	0.06
15-18 yrs/M	0.03	0.03	0.05
15-18 yrs/F	0.02	0.02	0.05
Adults (1986/7) 16-24 yrs/M	0.03	0.03	0.05
16-24 yrs/F	0.03	0.02	0.04
25-34 yrs/M	0.03	0.02	0.04
25-34 yrs/F	0.02	0.02	0.05
35-49 yrs/M	0.03	0.02	0.05
35-49 yrs/F	0.03	0.02	0.05
50-64 yrs/M	0.03	0.02	0.04
50-64 yrs/F	0.03	0.02	0.07
Older people free-living in the community (1994/5) 65-74 yrs/M	0.02	0.02	0.04
65-74 yrs/F	0.03	0.02	0.04
75-84 yrs/M	0.02	0.02	0.04
75-84 yrs/F	0.02	0.02	0.05
85 and over/M	0.02	0.02	0.05
85 and over/F	0.02	0.02	0.05
Older people living in institutions (1994/5) 65-84 yrs/M	0.02	0.02	0.03
65-84 yrs/F	0.02	0.02	0.03
85 and over/M	0.02	0.02	0.04
85 and over/F	0.02	0.02	0.04

⁸ Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

⁹ Data includes intakes from prescribed thiamin supplements.

¹⁰ Intakes for infants aged 6-12 months are from food only.

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Table 3: Sources of thiamin in the diet¹¹

Food Type	Contribution of food types to average daily intake of thiamin	
	mg/day	% of total
Cereal and cereal products	0.634	38
- of which breakfast cereals	0.295	18
- of which white bread	0.163	10
Milk and milk products	0.074	4
Egg and egg dishes	0.010	1
Fat spreads	0.000	0
Meat and meat products	0.353	21
Fish and fish dishes	0.013	1
Vegetables, potatoes and savoury snacks	0.430	26
Fruits and nuts	0.022	1
Sugar, confectionery and preserves	0.016	1
Beverages	0.045	3
Miscellaneous	0.049	3
Total intake from food	1.65	100*
<i>Intake from dietary supplements</i>	<i>0.03</i>	<i>2</i>
Total intake from food and supplements	1.68	100

*Total allows for rounding

¹¹ NDNS: young people aged 4-18 years. 1997/8. 15-18 year group.

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Table 4: Thiamin intake from supplements¹²

<i>Age/sex</i>	Consumers of thiamin supplements		Thiamin intake from supplements (consumers only) (mg/day)		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<i>Infants (1986)</i> 6-12 mths/M&F	*	*	*	*	*
<i>Pre-school children (1992/3)</i> 1½-4½ yrs/M&F	77	5	0.7	0.7	0.0 – 1.7
<i>Young people (1997/8)</i> 4-6 yrs/M&F	17	5	0.5	0.4	0.0 – 0.9
7-10 yrs/M&F	13	3	0.6	0.5	0.0 – 1.4
11-14 yrs/M	5	2	0.4	0.2	0.1 – 0.6
11-14 yrs/F	3	1	1.4	1.1	1.0 – 2.0
15-18 yrs/M	4	2	1.5	1.5	0.5 – 2.0
15-18 yrs/F	8	4	0.8	0.7	0.1 – 1.4
<i>Adults (1986/7)</i> 16-64 yrs/M	44	4	7.6	1.2	0.2 – 142.9
16-64 yrs/F	90	8	4.5	1.2	0.0 – 150.0
<i>Older people free-living in the community (1994/5)</i> 65 and over/M	35	5	2.9	1.2	0.1 – 30.0
65 and over/F	42	7	16.4	1.2	0.0 – 300.0
<i>Older people living in institutions (1994/5)</i> 65 and over/M	4	2	1.8	0.2	0.0 – 5.0
65 and over/F	6	3	0.5	0.1	0.1 – 2.9

* No data available

¹² Data includes intakes from prescribed thiamin supplements.

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ANNEX 2 TO EVM/00/14

Table 3. Oral toxicity in humans

form	report/study type	dose	Duration	effect	Reference
thiamin/ thiamin hydrochloride/thiamin nitrate	case report – woman aged 47	10 g/day	2.5 weeks	headache, irritability, insomnia, rapid pulse, weakness, trembling	Mills 1941
not stated	anecdotal	500 mg/day	1 month	“no objective symptoms”	Hawk <i>et al</i> 1954
not stated	case-report – woman aged 55 who took 100 mg/day thiamin for 15 days	100 mg/day	Single dose 2 months later	?anaphylaxis and death	Acharya <i>et al</i> 1969
not stated	case report – thiamin-related contact dermatitis in a young woman working in a factory filling vials with various vitamin preparations	200 mg experimental provocation	Single oral dose	eczema flare up	Hjorth 1958
not stated	case report – young woman	17 mg/day ¹	NS	muscle tremor, rapid pulse, nervous hyperirritability	Mills 1941
not stated	case-report – male aged 25	NS	NS	thiamin-associated allergic encephalitis	Markiewicz and Uss 1970
not stated	double-blind, placebo controlled, randomised crossover supplementation study in Alzheimer’s patients	4 g/day increasing up to 8 g/day	up to 6 months	2/17 patients experienced nausea and indigestion at a level of 7 and 7.5 g/day	Meador <i>et al</i> 1993
not stated	a randomised double-blind study in alcoholics	3x100 mg/day	21 days	treatment was reported as well-tolerated	Kretschmar <i>et al</i> 1996

not stated	placebo-controlled, crossover, supplementation study in young women suffering from primary dysmenorrhea	100 mg/day	90 day	no reported adverse effects	Gokhale 1996
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Key Table 3:

¹ It is suggested that this dose should read 17 g (see paragraph 69)

Table 4. Acute, subchronic and chronic toxicity of orally administered thiamin in laboratory animals

form	species (sex M/F)	duration, administration	effect		reference
thiamin/thiamin hydrochloride	mouse	single, <i>p.o.</i>		LD50 ~ 5g/kg	Molitor 1942
not stated	“rodent”	single, <i>p.o.</i>	shock, muscle tremor, convulsions, respiratory disturbance, death	LD50 ~ 3 g/kg	US FDA 1974 *
not stated	rat	12 weeks, maternal diet prior to mating	no maternal toxicity, no effect on offspring	NOAEL 75 ppm (4-8 mg/kg bw/day) ^φ	Morrison and Sarett 1959
thiamin nitrate	NMRI mouse (F)	single dose, <i>p.o.</i>	no toxic effects	NOAEL 5000 mg/kg	Leuschner 1992
not stated	mouse	acute <i>p.o.</i>	“low toxicity”	NS	Aramaki <i>et al</i> , 1955**
not stated	Sprague-Dawley rat (M & F)	105 weeks, dietary	no toxic effects, no increase in tumour incidence	NOAEL 10,000 ppm (366 and 459 mg/kg bw/day in M&F, respectively)	Heywood <i>et al</i> 1985
not stated	Wistar rat (M)	6 months, dietary	no specific toxic effects	NOAEL 1000 ppm (~ 50 mg/kg bw/day)	Watanabe <i>et al</i> 1958**

Key Tables 4:

NS not stated in available source

^φ approximate conversion by present author

In each case the NOAEL was also the maximum dose tested

* as cited by Iber *et al*, 1982**as cited by Heywood *et al*, 1985

Table 5. Developmental toxicity of thiamin

form	species (sex M/F)	duration, administration	effect	NOAEL	reference
thiamin/thiamin hydrochloride	Wistar-King rat ICR mouse	Days 7- 14 of gestation, <i>i.p.</i>	no maternal toxicity, no effect on offspring	500 mg/kg/d	Hori <i>et al</i> , 1966
not stated	“rodent”	NS	no reprotoxic effects	50 mg/kg/d	US FDA (1974)*
not stated	rat	12 weeks, maternal diet prior to mating	no maternal toxicity, no effect on offspring	75 ppm (4-8 mg/kg/d) ^ϕ	Morrison and Sarett 1959

Key Tables 5:

NS not stated in available source

* as cited by Iber *et al*, 1982**as cited by Heywood *et al*, 1985^ϕ approximate conversion by present author

ANNEX 3 TO EVM/00/14/P

Thiamin (B₁) : Summary table of selected nutrition related information and existing guidance on regulations

Unit of usage	mg/day		mg/100 kcal	mg/100g
	Male	Female		
<i>UK DRV¹³ for adults (19-50+)</i>	mg/1,000 kcal	mg/1,000 kcal		
LRNI	0.23	0.23		
EAR	0.30	0.30		
RNI	0.40	0.40		
<i>Mean adult UK dietary intake from food (all sources)</i>				
Adults 16-64 years ¹⁴	1.70 (2.01)	1.24 (1.61)		
Adults 65 years and over ¹⁵				
free living	1.49 (1.56)	1.19 (1.73)		
institutionalised	1.34 (1.35)	1.14 (1.16)		
EU labelling RDA ¹⁶	1.4 mg			
Supplemental doses	0.3 – 100 mg/unit			
Regulations				
Infant formula ¹⁷			Not less than 40 µg/100 kcal	
Cereal-based baby foods ¹⁸			Not less than 100 µg/100 kcal	
Weight reduction ¹⁹				
whole daily diet replacement	1.1			
meal replacement	0.33/meal			
Bread and Flour Regulations ²⁰				Not less than 0.24
<i>Maximum total safe daily intake</i>	Up to 3000			
COMA 1991 ¹				
EHPM 1997 ²¹	Upper safe level 50			

¹³ Committee on Medical Aspects of Food and Nutrition Policy (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects 41. London: HMSO.

¹⁴ Dietary and nutritional survey of British adults. 1986/7

¹⁵ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹⁶ The Food Labelling Regulations 1996

¹⁷ The Infant Formula and Follow-on Formula Regulations 1995

¹⁸ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1997.

¹⁹ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

²⁰ The Bread and Flour Regulations 1998

²¹ Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.

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