OPINION OF THE SCIENTIFIC COMMITTEE ON FOOD ON THE TOLERABLE UPPER INTAKE LEVEL OF VITAMIN B1

(EXPRESSED ON 11 JULY 2001)

FOREWORD

This opinion is one in the series of opinions of the SCF on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Vitamin B_1 or Thiamine, formerly known as Aneurine, is 3-(4-amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium. The free vitamin is a base. It is isolated and synthesized and used in food supplements and in food fortifications as a solid thiazolium salt in the form of thiamine hydrochloride or thiamine mononitrate. The molecular weight of thiamine hydrochloride is 337.29 g per mol. It is soluble in water and stable to heat below pH 5.0 and destroyed rapidly at pH 7.0 or above by boiling. Thiamine forms esters at the hydroxyethyl side chain with various acids. The most important ones are Thiamine monophosphate (TMP), Thiamine pyrophosphate (TPP) and Thiamine triphosphate (TTP) (McCormick, 1988).

2. NUTRITIONAL BACKGROUND AND METABOLISM

Vitamin B_1 was the first vitamin identified in 1926 by Jansen and Donath working on the antiberiberi factor from rice bran extracts. Lack of vitamin B_1 causes the deficiency disease Beriberi already known in Chinese antiquity. Nowadays in the Western world the vitamin B_1 deficiency is mainly found as a consequence of extreme alcoholism and known as Wernicke-Korsakoff syndrome. It is for this reason that thiamine has become the only regularly administered parenteral vitamin supplement in hospital emergency departments.

Vitamin B_1 mainly acts in α-ketoacid decarboxylation (e.g. pyruvate, α-ketoglutarate and branched-chain α-ketoacid acids), in transketolation (e.g. among hexose and pentose phosphates), and possibly in nerve conduction.

Ingested thiamine is well absorbed. It involves two mechanisms; the first is an active rate-limited jejunal uptake mechanism (Thomson *et al*, 1972). When the active transport is saturated, at an intestinal concentration greater than 3 μmol.l^{-1}, there is passive uptake. However, above an oral intake of 5 mg vitamin B_1 absorption rapidly declines (Friedeman *et al*, 1948). In a study of Davis *et al* (1984) with healthy volunteers vitamin B_1 plasma levels rose only marginally (42%) compared to folate and pyridoxine (>1500%), while the vitamin was actively excreted in the urine for up to six hours following an oral test dose of 10 mg. Vitamin B_1 is phosphorylated when it crosses the intestinal epithelium, but enters the blood principally as free vitamin B_1 and diffuses down a concentration gradient in the liver, heart, kidneys, and brain. In the blood vitamin B_1 is distributed between the plasma (10%) and cells (90%). The physiological whole blood concentration of the phosphate ester is 20 to 75 μg.l^{-1}. It is poorly stored and it is eliminated mainly in the urine either unchanged or as several (about 20) metabolites (Ariaey-Nejad *et al*, 1970). Raising the serum level of the vitamin results in active urinary excretion on the basis of the creatinine clearance (mean thiamine/creatinine/ renal clearance ratio of 2.4). After an oral dose of vitamin B_1, peak excretion occurs in about 2 hours and is nearly complete after 4 hours (Levy and Hewitt, 1971), as was already described in the early ninety-forties (Najjar and Holt, 1940; McAlpine and Hills, 1941).

Based on these observations, it is concluded that the plasma concentration of vitamin B_1 is tightly controlled. This is partly explained by Thom (1983), who reported that 20-30% of plasma vitamin B_1 is protein bound, all of which appeared to be as pyrophosphate. All unbound vitamin B_1 is rapidly dephosphorylated to facilitate excretion of an excess of the vitamin.

Vitamin B_1 metabolism is especially sensitive to excess alcohol consumption since the absorption of vitamin B_1 is decreased and its excretion is increased by alcohol. Alcohol also inhibits the activation of vitamin B_1 to its co-enzyme form Thiamine Pyrophosphate ester (TPP) (McCormick, 1988).

A vitamin B_1 kinetic study has been performed by Royer-Morrot *et al* (1992) using pharmacological doses intramuscular or orally. Comparison of 250 mg p.o. every 12 hours versus 500 mg i.m. once a day for 11 days resulted in a steady state plasma vitamin B_1 concentration after 7 and 5.6 days, respectively. The mean elimination half-life value was calculated to be approximately 1.8 days. Biological half-life of the vitamin is probably in the range of 9 to 18 days (Ariaey-Nejad *et al*, 1970). Total vitamin B_1 content of the adult human has been estimated to be approximately 30 mg (McCormick, 1988).

Animal experiments have shown that the rate of vitamin B_1 utilisation depends on the amount of carbohydrate metabolised. Because the principal metabolic role is in energy-yielding metabolism the requirement is related to energy intake. Increased physical activity, pregnancy and lactation increase vitamin B_1 requirements because of greater energy need; but when expressed per MJ the requirement is constant, and this relationship does not vary in such circumstances or with age. Based on this evidence the population recommended intake (PRI) is set at 100 μg per MJ leading to average daily requirements of around 1.0 to 1.2 mg per day (SCF, 1993). For people with energy intakes of less than 8 MJ per day, a minimal vitamin B_1 intake of 0.8 mg per day is suggested.

Vitamin B_1 is found in a large variety of animal and vegetable products but at a relatively low level (<0.5 mg/100 g). Important sources of vitamin B_1 are lean pork, legumes and cereal grains (germ fraction). The Nutriscan EC food and nutrition intake study revealed mean daily intake levels of vitamin B_1 on an EC average of 1.2 mg per day for women, ranging from 1.0 mg per day (NL) to 1.8 mg per day (Portugal) (SCF, 1993). With these figures in this low energy intake group, vitamin B_1 intake is generally considered as adequate in relation to physiological needs.

Biochemical changes in vitamin B_1 status occur well before the appearance of overt signs of deficiency. A number of sensitive tests have been developed to evaluate the vitamin B_1 status mostly based on the activity of enzymes with vitamin B_1 as co-enzyme. Erythrocyte transketolase activity (ETK-activity) and the *in vivo* stimulation of ETK-activity with thiamine phosphate (α-ETK) are reasonable indicators of marginal deficiency (1.20-1.25, 15-24%, respectively) and deficiency (>1.25, ≥25%, respectively) (Schrijver, 1991; Brin, 1980). Furthermore measurement of vitamin B_1 concentration and its phosphorylated esters in blood and urinary excretion under basal conditions is used.

3. HAZARD IDENTIFICATION

3.1. Evidence of adverse effects in humans

Orally ingested vitamin B_1 has a long history of use as an oral supplement without reported adverse effects. Due to its therapeutic action in some frequently observed clinical syndromes, thiamine hydrochoride has been advised and used over a long period of time. There are no reports of adverse effects of oral thiamine, even at dosages of several hundred milligrams a day (SCOGS, 1978; DHEW, 1979; Marks, 1989).

Rare cases of allergic sensitivity are documented mostly in the ninety-forties and have occurred solely in patients who received repeated vitamin B_1 by parenteral route (Tetreault and Beek, 1956). A systematic toxicity study by Wrenn *et al* (1989) on the parenteral use of thiamine at a dose of 100 mg in 989 patients resulted in 0.1% major reactions such as general pruritus. All the reported clinical symptoms suggest an anaphylactic reaction to the vitamin B_1 injection. Symptoms listed include anxiety, pruritus, nausea, respiratory distress, shock and in rare cases death (RDA Committee, 1998). Parenteral doses greater than 400 mg of vitamin B_1 cause nausea, anorexia, lethargy, mild ataxia and a diminution of gut tone (McCormick, 1988). More recent high level studies argue for inherently low toxicity of vitamin B_1 supplementation intravenously and especially orally. Royer-Morrot *et al* (1992) injected 500 mg daily intra-muscularly and reported one case of pruritus disappearing after 6 days of injection. Oral intake of two times 250 mg daily for 11 days did not reveal any adverse effects. Oral doses of 500 mg taken daily for a month did not lead to any adverse effects (Hawk *et al*, 1954).

Of interest is a study about vitamin intake in professional cyclists (Saris *et al*, 1989). This group is well known for their continuous massive intake of vitamins over years. Based on detailed questionnaires and product information, extra intake of vitamin B_1 was calculated to be 30 mg per day orally and 10 mg i.m. Plasma vitamin B_1 values were 237 $nmol.l^{-1}$ (reference value 95-138 $nmol.l^{-1}$) α-ETK was 1.02 (reference value 1.05-1.20). No adverse effects were reported.

A Medline search from 1966 on did not reveal any report on adverse effects after oral intake of vitamin B_1.

3.2. Toxicological data in animals

Lang (1979) reported that in all types of animal tests in his institute with extreme high oral doses of vitamin B_1, they never succeeded to detect any harmful effect. This was also the case under stress-related conditions such as iron deficiency or protein deficiency and using fifty times the normal daily doses of vitamin B_1. Only in one experiment with high vitamin B_1 intake and extreme low intake of protein and other B vitamins, effects were noticed probably caused by the unbalanced diet (Lang, 1979).

Bitsch (1997) reviewed the toxicity of vitamin B_1 given orally, and by intravenous or intraperitoneal injection and concluded that it is extremely safe. The tabulated LD_{50} levels in mice for thiamine hydrochloride were 0.07-0.125 g/kg bw intravenous, 0.317-0.500 g/kg bw intraperitoneal and 3-15 g/kg bw orally. Lang (1979) quoted an oral LD_{50} of vitamin B_1 of 3.0 g/kg bw for mice based on earlier studies of Hecht and Weese (1937). Symptoms by i.v. injections are hypotonia due to vasodilatation, bradycardia and respiratory arrhythmia leading to general neuromuscular inhibition. Death is caused by depression of the respiratory centre (Haley, 1948). The lethal i.v. dose in g/kg bw is for mice 0.125; rats 0.25; rabbits 0.30; and dogs 0.35 (McCormick, 1988). In monkeys up to 0.60 g/kg bw was required to produce toxic symptoms (Gubler, 1991). Similar pharmacological effects in humans are found only with parenterally administered doses hundreds of times larger than that required for optimal nutrition (Campbell *et al*, 1980). Rats have been maintained for three generations on oral doses of 0.08 to 1.0 mg/kg bw vitamin B_1 without any harmful effects (Williams and Spies, 1938). This is about 50 to 100 times the daily requirement. Gubler (1991) concluded that the margin between potential intake and levels of acute toxicity is at least 600 or more.

4. DOSE-RESPONSE ASSESSMENT AND DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

Due to the lack of systematic oral dose-response intake studies as well as the extreme low toxicity no LOAEL and NOAEL can be established.

5. CHARACTERISATION OF RISK

Since systematic data on adverse effects with oral intake of vitamin B_1 in human are very limited, an exposure assessment as given by the RDA (1998) can be of help. From the NHANES III data in the US, the highest mean intake of vitamin B_1 from food and supplements for any life-stage and gender group reported for males aged 31 through 50 years was 6.7 mg/day, the highest reported intake at 95th percentile was 11.0 mg/day for females aged 51 years and older. In table 1 intake data from a number of EU countries are given.

Table 1. Mean and high percentile vitamin B1 intake (mg/day) from food and supplements in some EU countries

Country	Type of survey	n	Method	Supplements*	Mean	97.5%
Italy[a]	household	2734	7-day weighed	+	1.10	1.90
Netherlands[b]	household	5958	2-day record	-	1.23	2.87
Austria[c]	individual	2488	24 h recall	-	1.36	3.55
Germany[d]	individual (M) individual (F)	4974 5304	7-day record 7-day record	- -	1.40 1.10	2.63 2.11
Ireland[e]	individual (M) individual (F)	662 717	7-day record 7-day record	+ +	2.28 2.13	4.65 6.35
UK[f]	individual (M) individual (F)	1087 1110	7-day weighed 7-day weighed	+ +	2.01 1.26	3.29 3.09

* + data included supplements; - data excluded supplements.
[a] Turrini (INRAN) [b] Hulshof and Kruizinga (1999)
[c] Elmadfa *et al* (1998) [d] Adolf *et al* (1995)
[e] IUNA (2001) [f] Gregory *et al* (1990)

The highest reported mean intake in the EU is 2.28 mg/day with a reported highest intake at 97.5 percentile of 6.35 mg/day. Both are considerably lower than the reported US values.

From the available literature it can be concluded that vitamin B_1 orally ingested has a very low risk of adverse effects. This is related to the fact that with intake levels higher than 5 mg absorption rapidly declines and absorbed vitamin B_1 is actively excreted in the urine. Therefore no adverse effects of orally ingested doses of vitamin B_1 have been reported despite the fact that relatively high doses of vitamin B_1 up to 50-200 mg daily have been used therapeutically over long periods of time (months) as well as the widely available supplements providing intakes up to 50 mg/day without prescription.

Based on parenteral use of vitamin B_1, reports show rare cases of adverse events at levels from 100 to 300 mg i.v. and more frequently at higher doses up to 500 mg i.v. daily.

A Canadian evaluation of micronutrient safety classified vitamin B_1 as a nutrient with no known adverse effects (Program on Food Safety, 1996). The Dutch Nutrition Council reported 500 mg as an upper safe limit (Nutrition Council RDA, 1989) as did the US RDA Committee in 1989. However in the latest report of the US Food and Nutrition Board (1998) no UL could be derived based on the inadequate data. The SCF (1993) mentioned no evidence of toxicity at oral intakes up to 500 mg/day (for 1 month).

Based on the presented evidence, the Committee comes to the conclusion that 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.

6. REFERENCES

Adolf T, Schneider R, Eberhardt W, Hartmann S, Herwig A, Heseker H, Hünchen K, Kübler W, Matiaske B, Moch KJ, Rosenbauer J (1995). Ergebnisse der Nationalen Verzehrsstudie (1985-1988) über die Lebensmittel- und Nährstoffaufnahme in der Bundesrepublik Deutschland. Band XI. VERA-Schriftenreihe (Herausgeber: W. Kübler, H.J. Anders, W. Heeschen), Wissenschaftlicher Fachverlag Dr. Fleck, Niederkleen, ISBN 3-930600-28-5.

Ariaey-Nejad MR, Balaghi M, Baker EM, Sauberlich HE (1970). Thiamine metabolism in man. Am J Clin Nutr 23: 764-778.

Bitsch R (1997). Vitamin B_1 (Thiamine). In: *Vitamin, Physiology, Pathophysiology, and Therapy*. Biesalski H.K., Weber, Schrezenmeir J., Weiss H.E., eds. Georg Thieme Verlag, Stuttgart, pp 65-74.

Brin M (1980). The functional evaluation of vitamin status with special attention to enzyme-coenzyme techniques. In: *Nutrition and Food Sciences. Nutritional biochemistry and pathology*. Santo W. *et al*, eds. Plenum Press NY, Vol 3 pp 131-153.

Campbell TC, Allison RG, Car CJ (1980). Feasibility of identifying adverse health effects of vitamins and essential minerals in man. Life Science Research Office FASEB, Bethesda, USA.

Davis RE, Icke GC, Thom J, Riley WJ (1984). Intestinal absorption of thiamin in man compared with folate and pyridoxal and its subsequent urinary excretion. J Nutr Sci Vitaminol 30: 475-482.

DHEW (1979). Vitamin and drug products for over-the-counter human use. Federal Register 44: 16126-16201.

Elmadfa I, Burger P, Derndorfer E, Kiefer I, Kunze M, König J, Leimüller G, Manafi M, Mecl M, Papathanasiou V, Rust P, Vojir F, Wagner K-H and Zarfl B (1998). Austrian Study on Nutritional Status (ASNS). Österreichischer Ernährungsbericht. Bundesministerium für Gesundheit, Arbeit und Soziales. Wien 1999.

Friedeman T, Kmieciak T, Keegan P, Scheft B (1948). The absorption, destruction and excretion of orally administered thiamine by human subjects. Gastroenterology 11: 100-103.

Gregory J, Foster K, Tyler H, Wiseman M (1990). The Dietary and Nutrtional Survey of British Adults. HMSO, London.

Gubler CJ (1991). Thiamin. In: Handbook of vitamins. Machlin IJ ed. Marcel Dekker NY, pp 233-281.

Haley TJ (1948). Parenteral thiamine hydrochloride toxicity. Proc Soc Exp Biol Med 68: 153.

Hawk PD, Oser BL, Summerson WH (1954). Vitamins and deficiency diseases. In: Practical Physiological Chemistry. Blakiston Comp. Inc. NY, pp 1194-1296.

Hecht G and Weese H (1937). Pharmakologisches über Vitamin B1 (Betaxin). Klin Wschr 16: 414-416.

Hulshof KFAM and Fruizinga AG (1999). Third Dutch National Food Consumption Survey (DNFCS-3) 1997-1998. TNO Zeist.

IUNA (Irish Universities Nutrition Alliance) (2001). The North/South Ireland Food Consumption Survey. Food Safety Promotion Board, Dublin. http://www.iuna.net

Lang K (1979). Biochemie der Ernährung. Dietrich Steinkopff, Verlag Darmstadt pp 470-486.

Levy G, Hewitt RR (1971). Evidence in man for specialized intestinal transport mechanisms for riboflavin and thiamine. Am J Clin Nutr 24: 401-404.

McAlpine D, Hill GM (1941). The clinical value of thiochrome test for aneurin (vitamin B_1) in urine. Quart J Med 34: 31-39.