# Risk Assessment — Thiamin (Vitamin $B_1$)

## General Information

### Chemistry

Thiamin (vitamin $B_1$) 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 triphosphate forms and the synthetic hydrochloride and slightly less water-soluble mononitrate salt. Synthetic non water-soluble derivatives of thiamin are available but these are not used in food supplements.

### Occurrence in food, food supplements and medicines

Foods providing rich sources of thiamin include unrefined grain products, meat products, vegetables, dairy products, legumes, fruits and eggs. 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, to replace losses during production; thus, cereal products are also a rich source of thiamin.

Mononitrate or hydrochloride derivatives of thiamin are present in multi-constituent medicinal products for the prevention (dose 1 – 5 mg daily) or treatment (dose 10 – 35 mg daily) of nutrient deficiencies. Supplements containing thiamin alone are also available (daily doses up to 300 mg).

### Recommended amounts

Body stores of thiamin are limited and a regular intake is necessary. Thiamin requirement is related to energy consumption. The RNI for adults and children ⩾ 1 year is 0.4 mg/1000 kcal and 0.3 mg/1000 kcal in infants (COMA, 1991). Assuming food intakes of 2000 kcal/day and 20% losses through cooking, this can be estimated to be 1.4 and 1 mg/day for adult males and females respectively. In pregnancy and lactation, thiamin requirement increases to approximately 1.6 – 1.8 mg/day.

### Analysis of tissue levels and thiamin status

Thiamin status may be assessed by measurement of thiamin levels in blood or by urinary excretion, before and after loading. Erythrocyte transketolase (ETK) activity or its activation coefficient (ATK-AC) in haemolysed red blood cells is a functional measure of thiamin status.

### Brief overview of non-nutritional beneficial effects

No reports of non-nutritional beneficial effects have been identified. Established therapeutic uses of thiamin supplements are largely related to the treatment or prophylaxis of deficiency. The effects of thiamin on spasmodic dysmenorrhoea, exercise performance, ventricular function, Alzheimer's disease, and leg cramps during pregnancy have been investigated, with inconclusive results.

## Function

Thiamin pyrophosphate (TPP) is a co-enzyme in several enzymatic reactions. TPP may also have a non-co-enzymic function during stimulation of neuronal cells and other excitable tissues, such as skeletal muscle.

## Deficiency

The biological half-life of thiamin is approximately 10 – 20 days and marginal deficiency can develop quite rapidly. Symptoms of sub-clinical deficiency include headache, tiredness, anorexia and muscle wasting. A regular daily thiamin intake of ⩽ 0.2 mg/1000 kcal results in clinical 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's encephalopathy, characterised by confusion, ataxia and coma. This condition is sometimes accompanied by a syndrome known as Korsakoff psychosis. Both conditions are typically found in alcoholics and co-exist in Wernicke-Korsakoff syndrome. In developed countries, most cases of thiamin deficiency are associated with chronic alcoholism where dietary intake of the vitamin may be low and absorption and utilisation impaired.

Thiamin deficiency may also be involved in foetal alcohol syndrome, characterised by growth retardation, psychomotor abnormalities and congenital malformations, in the offspring of alcoholic mothers.

## Interactions

Alcohol can impair the uptake and utilisation of thiamin and these effects may contribute to the prevalence of thiamin deficiency in alcoholics. Alcohol also reduces cellular thiamin diphosphokinase activity. Thiamin is an acetylcholine antagonist, and thus may enhance the effect of neuromuscular blocking agents. 5-Fluorouracil appears to be antagonistic to thiamin, possibly through competition for phosphorylation, which is required by both entities for their activation.

## Absorption and bioavailability

Thiamin in food appears to be highly available for absorption. Absorption of thiamin hydrochloride and other water-soluble forms 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.

## Distribution and metabolism

In the blood and tissues, thiamin is present as the free form and mono-, di- (pyro) and triphosphorylated 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. Liver contains the highest concentration of thiamin. Catabolic metabolism amounts to approximately 1 mg/day, and most of this occurs in the liver. The mean thiamin content of human breast milk in the UK has been reported to be 0.16 mg/L.

## Excretion

Thiamin metabolites and thiamin in excess of requirements are excreted in the urine. The level of unchanged thiamin in the urine increases as intake increases.

# Toxicity

## Human data

The oral toxicity of thiamin and thiamin derivatives in humans is generally considered very low. Most reports of adverse effects with exposure to thiamin follow parenteral nutrition. High oral doses of thiamin hydrochloride (⩾ 7000 mg) may cause headache, nausea, irritability, insomnia, rapid pulse and weakness. 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 from case reports. Three 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[14]. In another case, a patient suffered an anaphylactic reaction and subsequently died following a single oral dose of 100 mg thiamin 2 months after repeatedly taking 100 mg thiamin per day for a period of 15 days. One patient with thiamin-related contact dermatitis experienced an exacerbation of eczema following experimental provocation with an oral dose of 200 mg thiamin. A fourth case-report involved a young man who contracted allergic encephalitis following an oral dose of thiamin (the amount and form are unclear).

No evidence has been identified on reproductive effects of thiamin or thiamin derivatives in humans.

*Supplementation trials*

In a supplementation study, one isolated individual, who had earlier received parenteral thiamin hydrochloride, experienced nausea and insomnia following a daily dose of 200 mg thiamin hydrochloride per day for less than a week. Symptoms resolved when the dose was halved.

## Animal data

The animal toxicity database is limited. Thiamin is of low acute toxicity but single oral doses of 3000-5000 mg/kg bw thiamin/thiamin hydrochloride in rats and mice are lethal. Thiamin nitrate is even less acutely toxic, with no adverse effects being reported in mice following a single oral dose of 5000 mg/kg bw. There is an absence of chronic and sub-chronic data for high-dose exposure to the water-soluble thiamin derivatives.

## Carcinogenicity and genotoxicity

There has been no study on the carcinogenicity of thiamin. Thiamin hydrochloride has been shown to be non-mutagenic in a range of bacterial mutagenicity and *in vitro* chromosomal aberration tests.

## Genetic variations

There are no known genetic variations resulting in increased susceptibility to thiamine toxicity.

[15] It is noted that a dose of 17 mg would have been inconsistent with the rate of urinary and likely faecal excretion quoted within the original article. It is suggested, therefore, that this was a text error within the article that should have read '17 g', equivalent to 17,000 mg.

### Mechanisms of toxicity

No mechanisms of toxicity have been identified.

### Dose-response characterisation

No data have been identified.

### Vulnerable groups

No vulnerable groups have been identified; however, the clinical trials indicate that there is a possibility that a very small number of people may be particularly sensitive (allergic) to thiamin.

## Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

### Human data

*Mills, 1941*

Thiamin-associated toxicity was reported in a 47 year old woman who had been taking 10,000 mg thiamin hydrochloride daily for $2^{1}/_{2}$ weeks (presumably by the oral route, although this is unclear). 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 $4^{1}/_{2}$ weeks after the patient resumed a dose of 5 mg per day[16]. Again, prompt relief soon followed cessation of intake. 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 woman receiving an average of 17 mg thiamin hydrochloride per day (again, this was presumed to be by mouth but this was not explicit)[17]. The woman was said to be excreting 12 mg/day in her urine and passing stools smelling strongly of thiamin.

*Meador et al., 1993*

This was a study conducted in 17 Alzheimer's patients (9 males and 8 females), mean age 69 years, to assess possible beneficial effects of thiamin supplementation. Patients were treated with graduated doses of thiamin hydrochloride, up to 6000-8000 mg/day, for 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 7000 and 7500 mg/day. However, these individuals were subsequently returned to their own previously highest tolerated doses (6500 and 7000 mg/day) without side effects. The study was limited in that there were small numbers involved and that 8/17 subjects suffered significant mental impairment on objective mental tests, so that any effects may have been undereported.

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

[17] The dose reported here as 17 mg is inconsistent with the quoted rate of urinary and likely faecal 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 notes 15 and 16).

*Gokhale, 1996*

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. The thiamin status of the participants is unclear. A daily oral dose of 100 mg of thiamin hydrochloride was given for 90 days followed by placebo for 60 days or vice versa. No adverse effects were reported.

### Animal data

*Molitor, 1942*

The lethal dose for thiamin in mice was reported to be 100 mg (approximately 5000 mg/kg bw, assuming a bodyweight of 20 g).

*Leuschner, 1992*

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 (weight, 21 – 28 g) when administered oral doses of thiamin nitrate in 0.8% aqueous hydroxypropyl methylcellulose gel at doses up to 5000 mg/kg bw. The number of animals tested was not stated.

## Exposure assessment

Total exposure/intake:

| | |
|---|---|
| Food | Mean: 1.50 mg/day (from 1986/87 NDNS)<br>97.5th percentile: 2.6 mg/day |
| Supplements | up to 300 mg/day (OTC, 2001) |
| Estimated maximum intake: | 2.6 + 300 = 303 mg/day |

No potential high intake groups have been identified.

## Risk assessment

Thiamin present in food is efficiently absorbed. However, water-soluble supplements, such as thiamin hydrochloride and thiamin mononitrate, are poorly absorbed due to saturation of transport mechanisms.

It is generally accepted that ingested thiamin has a very low toxicity in humans. Most data are either in the form of case reports of possible thiamin-associated adverse effects or from thiamin supplementation studies designed primarily to investigate potential beneficial effects. The latter do not always specifically report an absence of adverse effect.

The limited amount of human data indicates that adverse effects are generally CNS-related and occur only at very high doses. A small number of individuals may show an allergic response to lower doses,

but reports of these lower dose-related events are rare. It is possible that this sub-population may be the same sub-group that is susceptible to adverse effects, e.g. anaphylaxis etc, following parenteral administration of thiamin.

The animal database is also very limited. A lethal dose of thiamin in rodents is preceded by CNS effects such as shock, muscle tremor, convulsions, respiratory disturbance and collapse, symptoms which are similar to acute thiamin toxicity in humans.

## ESTABLISHMENT OF GUIDANCE LEVEL

There are insufficient data to establish a Safe Upper Level for thiamin. The oral toxicity of thiamin and thiamin derivatives in humans is generally considered to be very low. Most available documented data are either in the form of case reports of possible thiamin-associated adverse effects or from thiamin supplementation studies designed primarily to investigate potential beneficial effects. The latter generally involve the use of the synthetic non-water soluble derivatives (not included in this review and not currently found in dietary supplements) and do not always specifically report an absence of adverse effect. Reports of thiamin-associated toxicity in humans are rare and most relate to incidents following parenteral administration of the vitamin. High doses ($\geqslant$ 5000 mg) of thiamin hydrochloride may cause headache, nausea, irritability, insomnia, rapid pulse and weakness; 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.

No specific toxic effects of thiamin ingestion by humans have been identified. However, there is a paucity of large controlled human supplementation studies. Significant adverse effects have not been noted with the water-soluble forms of thiamin used in dietary supplements. These forms are poorly absorbed at high doses, which further restricts their toxicity.

One human supplementation study (Meador *et al*., 1993) reported that graduated doses of thiamin hydrochloride, up to 6000-8000 mg/day for 5-6 months, caused no adverse effects in a very small group of patients. These subjects were reported to have tolerated the doses well, without weakness or other side effects, with the exception of two subjects (out of seventeen) who developed nausea and indigestion at doses of 7000 – 7500 mg. The study may well have under-reported side effects since half of the subjects were suffering from significant mental impairment on objective measures. From the available database, it appears that higher doses of thiamin ($\geqslant$ 7000 mg) may be associated with headache, nausea, irritability, insomnia, rapid pulse and weakness.

In a randomised double-blind placebo-controlled study by Gokhale *et al*. (1996), a daily oral dose of 100 mg thiamin hydrochloride (for sixty or ninety days) was given to 556 young females (12 – 21 years). No adverse effects were reported. The thiamin status of the participants is unclear. Based on this study, a level of 100 mg/day (equivalent to 1.7 mg/kg supplemental thiamin for a 60 kg adult) of supplemental thiamin would not be expected to result in adverse effects. No uncertainty factor has been applied since this guidance is based on human data with large numbers of subjects and no hazard has been identified from other studies. This level is for guidance only and is applicable to the water-soluble forms of thiamin only. It should be noted that the applicability of the study, which was conducted in young women, to the general population is uncertain and the possibility of rare hypersensitivity reactions cannot be excluded.

## References

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