4
Thiamin

SUMMARY

Thiamin functions as a coenzyme in the metabolism of carbohydrates and branched-chain amino acids. The method used to estimate the Recommended Dietary Allowance (RDA) for thiamin combines erythrocyte transketolase activity, urinary thiamin excretion, and other findings. The RDA for adults is 1.2 mg/day for men and 1.1 mg/day for women. Recently, the median intake of thiamin from food in the United States was approximately 2 mg/day, and the ninety-fifth percentile of intake from both food and supplements was approximately 6.1 mg. Intakes in two Canadian populations were slightly lower. Data concerning adverse effects are not sufficient to set a Tolerable Upper Intake Level (UL) for thiamin.

BACKGROUND INFORMATION

Thiamin (also known as vitamin B_1 and aneurin) was the first B vitamin identified. Lack of thiamin causes the deficiency disease called beriberi, which has been known since antiquity. More recently, at least in industrialized nations, thiamin deficiency has been mainly found in association with chronic alcoholism, where it presents as the Wernicke-Korsakoff syndrome.

Chemically, thiamin consists of substituted pyrimidine and thiazole rings linked by a methylene bridge. It exists mainly in various interconvertible phosphorylated forms, chiefly thiamin pyrophosphate

(TPP). TPP, the coenzymatic form of thiamin, is involved in two main types of metabolic reactions: decarboxylation of α-ketoacids (e.g., pyruvate, α-ketoglutarate, and branched-chain keto acids) and transketolation (e.g., among hexose and pentose phosphates).

Physiology of Absorption, Metabolism, and Excretion

Following ingestion, absorption of thiamin occurs mainly in the jejunum, at lower concentrations as an active, carrier-mediated system involving phosphorylation and at higher concentrations by passive diffusion. Thiamin is transported in blood both in erythrocytes and plasma.

Only a small percentage of a high dose of thiamin is absorbed, and elevated serum values result in active urinary excretion of the vitamin (Davis et al., 1984). After an oral dose of thiamin, peak excretion occurs in about 2 hours, and excretion is nearly complete after 4 hours (Levy and Hewitt, 1971; Morrison and Campbell, 1960). In a study by Davis and colleagues (1984), a 10-mg oral dose of thiamin was given in water, and the mean serum thiamin peaked at 24 nmol/L (7.2 μg/L)—42 percent above baseline. Within 6 hours the serum thiamin concentration had returned to baseline, 17 nmol/L (5.2 μg/L). Prompt urinary excretion of thiamin was also reported by Najjar and Holt (1940) and McAlpine and Hills (1941).

With higher pharmacological levels, namely repetitive 250-mg amounts taken orally and 500 mg given intramuscularly, nearly 1 week was required for steady state plasma concentrations to be reached; a mean elimination half-life of 1.8 days was estimated (Royer-Morrot et al., 1992).

Total thiamin content of the adult human has been estimated to be approximately 30 mg, and the biological half-life of the vitamin is probably in the range of 9 to 18 days (Ariaey-Nejad et al., 1970).

Clinical Effects of Inadequate Intake

Early stages of thiamin deficiency may be accompanied by nonspecific symptoms that may be overlooked or easily misinterpreted (Lonsdale and Shamberger, 1980). The clinical signs of deficiency include anorexia; weight loss; mental changes such as apathy, decrease in short-term memory, confusion, and irritability; muscle weakness; and cardiovascular effects such as an enlarged heart (Horwitt et al., 1948; Inouye and Katsura, 1965; Platt, 1967; Williams et al., 1942; Wilson, 1983). In wet beriberi, edema occurs; in dry

beriberi, muscle wasting is obvious. In infants, cardiac failure may occur rather suddenly (McCormick and Greene, 1994). Severe thiamin deficiency in industrialized countries is likely to be related to heavy alcohol consumption with limited food consumption, as was noted for at least four of five Welsh cases reported by Anderson and colleagues (1985). In those cases renal and cardiovascular complications were life threatening.

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR THIAMIN

Biochemical changes in thiamin status occur well before the appearance of overt signs of deficiency. Thiamin status can be assessed by determining erythrocyte transketolase activity, by measuring the concentration of thiamin and its phosphorylated esters in blood or serum components using high-performance liquid chromatography, or by measuring urinary thiamin excretion under basal conditions or after thiamin loading. Commonly used reference values indicating marginal deficiency for these indicators are given in Table 4-1. Other methods have also been reported and are covered briefly below.

No currently available indicator, by itself, provides an adequate basis on which to estimate the thiamin requirement.

Urinary Thiamin Excretion

The urinary excretion of thiamin is the indicator that has been used most widely in metabolic studies of thiamin requirements and

TABLE 4-1 Reference Values for the Primary Measures of Thiamin Status

Indicator	Marginal Deficiency	Deficiency
Erythrocyte transketolase activity[a]	1.20–1.25	> 1.25
Erythrocyte thiamin (nmol/L)[a]	70–90	< 70
Thiamin pyrophosphate effect (%)[b]	15–24	≥ 25
Urinary thiamin[a]		
(nmol [μg]/g creatinine)	90–220 (27–66)	< 27
(nmol [μg]/d)	133–333 (40–100)	< 40

[a] Schrijver (1991).

[b] Stimulated value, expressed as a multiple of the basal value. Also termed the activity coefficient. Brin (1970).

was thus given careful consideration in deriving the Estimated Average Requirement (EAR). Urinary thiamin excretion decreases markedly as thiamin status declines and is also affected by recent dietary intake. Bayliss and coworkers (1984) reported a correlation of 0.86 between the oral dose of thiamin and urinary thiamin excretion. However, in doses of up to 1.05 mg there was overlap with baseline values. The use of a load test, in which thiamin excretion is measured before and after a test load of thiamin, helps differentiate between extremes of vitamin status (McCormick and Greene, 1994).

Erythrocyte Transketolase Activity

Erythrocyte transketolase activity has also been widely used and is generally regarded as the best functional test of thiamin status (McCormick and Greene, 1994), but it has some limitations for deriving the EAR and should be evaluated along with other indicators. In this test, erythrocytes are lysed and the transketolase activity is measured before and after stimulation by the addition of thiamin pyrophosphate (TPP); the basal level and the stimulated value (typically expressed as a multiple of the basal level, termed the activity coefficient or TPP effect) are measured. In thiamin-depleted individuals, basal erythrocyte transketolase typically is low and the incremental response after TPP addition is enhanced.

Although the test has long been used in assessing thiamin status, in one recent study (Bailey et al., 1994) it correlated poorly with dietary thiamin intake in English adolescents. Similarly, in a study population of 179 adult men, Gans and Harper (1991) found a wide range of TPP effect values (0 to 95 percent) associated with thiamin intakes that were all above 1.5 mg/day over a 3-day period. Similarly, they also found a TPP effect of 0 percent associated with a wide range of intakes (approximately 0.75 to 6.0 mg/day). Schrijver (1991) reported that the activity coefficient may appear normal after prolonged deficiency, making identification of the deficiency more problematic. From studies of the elderly, Pekkarinen and colleagues (1974) concluded that evaluation of thiamin status should consider other indicators along with erythrocyte transketolase activity.

Factors other than thiamin status, such as genetic defects, may influence the enzyme activity and thus the test results. Individuals and tissues both differ in their sensitivity to thiamin deficiency. This observation may be explained by the pronounced lag in the formation of active holoenzyme and the interindividual and cell type variation in the lag during thiamin deficiency (Singleton et al., 1995).

Erythrocyte Thiamin

As thiamin status declines, the concentration of TPP in erythrocytes decreases at approximately the same rate as occurs in other tissues (Brin, 1964; McCormick and Greene, 1994). The TPP effect may be noted within 2 weeks after the initiation of a thiamin-restricted diet (Brin, 1962). Baines and Davies (1988) provided evidence that, compared with erythrocyte transketolase activity, erythrocyte TPP is more stable in frozen erythrocytes, easier to standardize, and less susceptible to factors that influence enzyme activity.

Other Measurements

Because of the wide variety of signs and symptoms characteristic of thiamin deficiency, numerous other indicators of thiamin status have been reported. These include blood pyruvic acid values after exercise (Foltz et al., 1944); both pyruvic acid and lactic acid values after administration of glucose (Bueding et al., 1941; Williams et al., 1943); various indicators of work performance (e.g., maximum work test to exhaustion) (Wood et al., 1980); aerobic power, respiratory exchange ratio, and ventilatory equivalent (van der Beek et al., 1994); work output over time (Foltz et al., 1944); gross behavior changes (Williams et al., 1942); neurological changes (Wood et al., 1980); psychological changes (Wood et al., 1980); and quality of life (Wilkinson et al., 1997). None of these was judged to be a dependable criterion of thiamin status.

FACTORS AFFECTING THE THIAMIN REQUIREMENT

Bioavailability

Data on the bioavailability of thiamin in humans are extremely limited. Levy and Hewitt (1971) reported that absorption of thiamin supplements taken with breakfast does not differ from that taken on an empty stomach. No adjustments for bioavailability were judged necessary for deriving the Estimated Average Requirement (EAR).

Energy Intake

No studies were found that examined the effect of energy intake on the thiamin requirement. Some studies provided thiamin in

graded doses that kept the ratio of thiamin to energy constant for those studied who had different energy requirements. Other studies provided total amounts of thiamin (and sometimes energy) that were the same for all individuals. Sauberlich and colleagues (1979) adjusted activity levels rather than energy intake to maintain weight in their subjects. Several investigators examined their data to assess whether it would be better to express thiamin as an absolute value or in relation to energy. For example, Dick and colleagues (1958) reported that the coefficient of variation of the estimated thiamin requirement for adolescent boys was 14.2 percent/person, 15.5 percent/1,000 kcal, 27.5 percent/kg body weight, 19.5 percent/m^2 surface area, and 19.2 percent/mg of creatinine excretion. Elsom and coworkers (1942) noted that they could not distinguish whether it was better to express thiamin in absolute values or per 1,000 kcal but that thiamin intake expressed per body weight did not discriminate between those who were deficient and those who were not. Anderson and colleagues (1986) presented evidence that expressing the thiamin requirements in absolute terms is more useful for predicting biochemical thiamin status than expressing it in relation to energy intake, and data from individuals presented by Henshaw and coworkers (1970) appear supportive.

Despite the lack of direct experimental data, the known biochemical function of thiamin as thiamin pyrophosphate (TPP) in the metabolism of carbohydrate suggests that at least a small (10 percent) adjustment to the estimated requirement to reflect differences in the average energy utilization and size of men and women, a 10 percent increase in the requirement to cover increased energy utilization during pregnancy, and a small increase to cover the energy cost of milk production during lactation may be necessary. It has been observed that during periods of starvation such as in war, larger individuals present signs of beriberi more rapidly than do those with smaller body builds, indicating their greater needs for thiamin and other energy-related nutrients (Burgess, 1946). Many studies report thiamin intake per 1,000 kcal; others report total intake. Thus, the evidence below is presented as it was done in the studies and not because the ratio is considered important.

Physical Activity

Heavy exercise under certain conditions may increase the requirement for thiamin as well as other vitamins, but the observations on the effects of physical activity on the thiamin requirement have been inconsistent, the effects small, and the experimental conditions

highly variable. For example, one 14-week, double-blind, $2 \times 2 \times 2$ complete factorial experiment examined the effects of restriction of three vitamins—thiamin, riboflavin, and vitamin B_6—on physical performance in 24 healthy Dutch males (van der Beek et al., 1994). In the thiamin-restricted group, thiamin intake was 0.43 mg/day (analyzed mean value). Thiamin concentration, erythrocyte transketolase activity, and urinary thiamin decreased significantly over the 11-week experimental period, and α-erythrocyte transketolase activity (or activation coefficient) increased. The decrease in thiamin status was accompanied by small but significant decrements in performance as measured during single short bouts of intense exercise, but these could not be attributed to any one of the three vitamins studied.

In another double-blind study, 12 mg of thiamin (15 mg of thiamin nitrate) along with riboflavin and pyridoxine were provided to all 22 subjects in the experimental group for 5 weeks. Although the activation coefficients for transketolase (and other enzymes) decreased in the supplemented group, no change in blood lactate was found after exercise (Fogelholm et al., 1993).

An observational study (Folgeholm et al., 1992) that found comparable erythrocyte transketolase activation coefficients in skiers and nonskiers provided little useful information on the effect of energy expenditure on thiamin requirements. Compared with the nonskiers, the skiers had much higher energy intakes and expenditures along with much higher intakes of all reported nutrients. For both males and females, mean thiamin intakes were 0.8 mg/1,000 kcal for the skiers and 0.7 mg/1,000 kcal for the control subjects.

It was thus concluded that under normal conditions, physical activity does not appear to influence thiamin requirements to a substantial degree. However, those who are engaged in physically demanding occupations or who spend much time training for active sports may require additional thiamin.

Gender

Studies were not found that directly compare the thiamin requirements of males and females. A small (10 percent) difference in the average thiamin requirements of men and women is assumed on the basis of mean differences in body size and energy utilization.

FINDINGS BY LIFE STAGE AND GENDER GROUP

Infants Ages 0 through 12 Months

Method Used to Set the Adequate Intake

An Adequate Intake (AI) is used as the goal for intake by infants.

Ages 0 through 6 Months. The AI reflects the observed mean thiamin intake of infants consuming human milk. Thus, the thiamin AI for young infants is based on mean intake data from infants fed human milk exclusively during their first 6 months and uses the thiamin concentration of milk produced by well-nourished mothers. There are no reports of full-term infants who were exclusively fed milk from U.S. or Canadian mothers who manifested any signs of thiamin deficiency; however, infants breastfed by mothers with beriberi have been reported to develop beriberi themselves by age 3 to 4 weeks (Hytten and Thomason, 1961). The thiamin content of human milk was similar for well-nourished mothers who received vitamin supplements and for those who did not (Nail et al., 1980; Pratt and Hamil, 1951).

The thiamin concentration is low in colostrum (approximately 0.01 μg/L). The mean concentration of thiamin in mature human milk is 0.21 ± 0.04 mg/L (mean ± standard deviation) (Committee on Nutrition, 1985). Using the mean volume for intake of human milk of 0.78 L/day (see Chapter 2) and the average thiamin content of 0.21 mg/L, the AI for thiamin is 0.16 mg/day for infants ages 0 through 6 months, which is rounded to 0.2 mg. For the reference infant weight of 7 kg, this corresponds to 0.03 mg/kg/day.

Blood concentration of total thiamin (phosphorylated and nonphosphorylated) has been shown to decrease with age: in a cross-sectional study of well-nourished individuals, blood thiamin concentrations in infants less than 3 months of age (n = 64) averaged 258 ± 63 nmol/L (75 ± 23 μg/L) (mean ± standard deviation), infants 3 to 12 months of age (n = 100) averaged 214 ± 44 nmol/L (64 ± 13 μg/L), while in children and young adults (n = 159) the value decreased to 187 ± 39 μmol/L (56 ± 12 μg/L) (Wyatt et al., 1991). Because total thiamin concentrations in whole blood and cerebrospinal fluid decrease in the first 12 to 18 months of life, age-specific norms should be used for determining thiamin status in infancy.

Ages 7 through 12 Months. If the reference body weight ratio method described in Chapter 2 to extrapolate from the AI for thiamin for infants ages 0 through 6 months is used, the AI for thiamin for the older infants would be 0.2 mg/day after rounding. The second method (see Chapter 2), extrapolating from the Estimated Average Requirement (EAR) for adults and adjusting for the expected variance to estimate a recommended intake, gives an AI of 0.3 mg of thiamin, a value higher than that obtained from the first method.

Alternatively, the AI for thiamin for infants ages 7 through 12 months could be calculated by using the estimated thiamin content of 0.6 L of human milk, the average volume consumed by this age group (thiamin content equals 0.13 mg), and adding the amount of thiamin provided by solid foods (0.5 mg), as estimated by Montalto et al. (1985) (see Chapter 2). The result equals approximately 0.6 mg/day. This value was judged to be unreasonably high because it is two to three times the extrapolated values given above. Thus the AI for thiamin is 0.3 mg/day for infants ages 7 through 12 months—the value extrapolated from estimates of adult requirements.

Thiamin AI Summary, Ages 0 through 12 Months

AI for Infants		
0–6 months	**0.2 mg/day of thiamin**	**≈0.03 mg/kg**
7–12 months	**0.3 mg/day of thiamin**	**≈0.03 mg/kg**

Children Ages 1 through 8 Years

Method Used to Estimate the Average Requirement

No direct data were found on which to base an EAR for children ages 1 through 8 years. In the absence of additional information, EARs and Recommended Dietary Allowances (RDAs) for these age groups have been extrapolated from adult values by using the method described in Chapter 2.

Thiamin EAR and RDA Summary, Ages 1 through 8 Years

EAR for Children	**1–3 years**	**0.4 mg/day of thiamin**
	4–8 years	**0.5 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the

RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Children	**1–3 years**	**0.5 mg/day of thiamin**
	4–8 years	**0.6 mg/day of thiamin**

Children and Adolescents Ages 9 through 18 Years

Evidence Considered in Estimating the Average Requirement

Five studies were found for this age group, none of which involved children younger than 13 years. In an observational study of 19 boys and 35 girls aged 13 or 14 years, thiamin intake was calculated from 7-day food records and was also analyzed by high-performance liquid chromatography from duplicate portions (Bailey et al., 1994). The correlations of the results from the food records and the analyses of duplicate portions were significant but moderate ($r = 0.59$ for boys and 0.43 for girls). However, the indicators of thiamin status (erythrocyte transketolase, erythrocyte transketolase activity coefficient, and total erythrocyte thiamin concentration) were not correlated with each other. Moreover, none of them was correlated with thiamin intake as estimated from the food records or measured in the duplicate portions. A substantial percentage of the subjects (girls, 12 percent; boys, 17 percent) had activity coefficients that indicated a high risk of thiamin deficiency according to Brin's criterion for adults (Brin, 1970) even though estimated intakes were above 0.4 mg/1,000 kcal.

A controlled-diet, dose-response experiment was conducted with nine girls aged 16 to 18 years to examine the thiamin requirement (Hart and Reynolds, 1957). In this study, the girls were given 0.29 mg of thiamin/1,000 kcal/day (0.63 mg/day total) for the first 16-day period and 0.6 mg/1,000 kcal/day (1.3 mg/day) for the second 16-day period. The adequacy of intake was assessed by measuring total daily thiamin excretion, the percentage of consumed thiamin that was excreted, the ratio of thiamin to creatinine in the urine, and the percentage of excretion of a 5-mg oral test dose of thiamin hydrochloride. Using a modification of the thiochrome method for thiamin determination, the investigators were unable to obtain reliable measurements of the amount of thiamin excreted on the low-thiamin diet. The authors noted that the subjects became irritable and uncooperative and lost the ability to concentrate when fed the low-thiamin diet—symptoms also noted by others in the early stage

of thiamin deficiency. On the diet that provided 1.3 mg/day of thiamin, 24-hour thiamin excretion ranged between 0.27 and 0.44 μmol (81 and 133 μg). These data suggest that the average thiamin requirement is less than 1.3 mg/day, especially considering the short period of repletion and the use of a generous cutoff point for urinary thiamin excretion, but they do not allow further refinement of the estimate.

In a study of eight boys aged 14 to 17 years, Dick and colleagues (1958) calculated thiamin requirements from a regression of excretion on intake at five levels of thiamin that ranged from 0.6 to 2.7 mg/day. By taking the abscissa of the intersection of two straight lines fitted to the observations on each subject, a mean requirement of 1.41 mg/day was computed. However, at this level of intake, mean urinary excretion averaged 0.618 μmol/day (186 μg/day)—a value far in excess of usual cutoffs.

In the absence of additional definitive information about requirements, EARs and RDAs for thiamin for these age groups were extrapolated from the adult values by using the method described in Chapter 2. Because only urinary excretion of thiamin was measured, the results reported by Hart and Reynolds (1957) are not considered strong enough to warrant adjustment of results from the extrapolation method.

Thiamin EAR and RDA Summary, Ages 9 through 18 Years

EAR for Boys	**9–13 years**	**0.7 mg/day of thiamin**
	14–18 years	**1.0 mg/day of thiamin**
EAR for Girls	**9–13 years**	**0.7 mg/day of thiamin**
	14–18 years	**0.9 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Boys	**9–13 years**	**0.9 mg/day of thiamin**
	14–18 years	**1.2 mg/day of thiamin**
RDA for Girls	**9–13 years**	**0.9 mg/day of thiamin**
	14–18 years	**1.0 mg/day of thiamin**

Adults Ages 19 through 50 Years

Indicators Used to Estimate the Average Requirement

It was necessary to review data from studies that used various indicators of thiamin sufficiency to derive an EAR for thiamin for adults. In reviewing the studies (Table 4-2), heavy weight was given to the carefully controlled, thiamin depletion-repletion experiment conducted with seven healthy young men (age not specified) in a metabolic unit (Sauberlich et al., 1979). The investigators concluded that thiamin at 0.30 mg/1,000 kcal (approximately 1.0 mg/day) met the minimum requirement for young men as determined by using urinary excretion of thiamin, and it appears that this value is close to the average requirement for normal erythrocyte transketolase activity. This value is slightly lower than the 1.2 and 1.0 mg total values designated by Anderson and colleagues (1986) as minimal for men and women, respectively, determined by using erythrocyte transketolase activity.

Studies by Bamji (1970) and Ziporin and coworkers (1965) support the conclusion that 0.30 mg/1,000 kcal/day is a minimum thiamin requirement to prevent overt signs and symptoms of deficiency, although at this level urinary excretion of thiamin was abnormal in some subjects. Studies by Kraut and colleagues (1966) and Reuter et al. (1967) suggest a much higher requirement. Although intakes of approximately 0.7 mg/day (0.4 mg/1,000 kcal) were found to meet the minimum requirement for thiamin based on erythrocyte transketolase activity (Reuter et al., 1967), the achievement of maximum erythrocyte transketolase activity required intakes of 2.0 to 2.5 mg/day (Kraut et al., 1966; Reuter et al., 1967). Several studies indicated that intakes of 0.075 to 0.29 mg/1,000 kcal lead to severe irritability and other symptoms and signs of deficiency (Foltz et al., 1944; Horwitt et al., 1948; Wood et al., 1980). Data are not sufficient to indicate differing requirements for adults 19 through 30 versus 31 through 50 years of age.

Thiamin EAR and RDA Summary, Ages 19 through 50 Years

Examination of the data in Table 4-2 indicates that the EAR for thiamin is at least 0.3 mg/1,000 kcal or 0.8 mg/day and that intakes greater than 1.0 mg are marginally adequate for normal erythrocyte transketolase activity and generally adequate for urinary thiamin excretion. Because of the uncertainties of the dietary intake estimates in the studies by Anderson et al. (1986) and Henshaw et al.

TABLE 4-2 Metabolic Studies Providing Evidence Used to Derive the Estimated Average Requirement (EAR) for Thiamin for Adults

Reference	Subjects	Duration of Study	Baseline Thiamin Intake
Elsom et al., 1942	9 women	28–120 d	0.8 mg/d 0.3 mg/d 0.7 mg/d NA NA NA NA NA NA
Foltz et al., 1944	4 men	1 mo 1 mo 9–12 mo	NA
Horwitt et al., 1948	24	3 y	1 mg/d
Ziporin et al., 1965	8 men	30 d depletion 12 d repletion	Mean intake during 9-d control period =1.75 mg/d
Kraut et al., 1966	4 men, 2 women	9–10 mo	NA
Reuter et al., 1967	6 obese women	NA	NA
Bamji, 1970	4 men, 4 women	2–3 wk depletion 1 wk repletion	0.1 mg/1,000 kcal (depletion level)
Henshaw et al., 1970	39 women	3 d 7 d	NA
Sauberlich et al., 1979	7 men	14 d 11 d 11 d 13 d	> 0.6 mg/1,000 kcal

Thiamin Intake During Repletion or Maintenance (mg/d)	Erythrocyte Transketolase Activity	Urinary Excretion of Thiamin	Other
0.2	NA[a]	Abnormal[b]	Abnormal[c]
0.2	NA	Abnormal	Abnormal
0.35	NA	Abnormal	Abnormal
0.41	NA	Abnormal	Marginal[d]
0.52	NA	Abnormal	Marginal
0.57	NA	Abnormal	Marginal
0.65	NA	Normal	Normal
0.70	NA	Normal	Normal
0.77	NA	Normal	Normal
0.57	NA	Abnormal[e]	Abnormal[f]
0.95	NA	50% normal	Abnormal[g]
1.44	NA	Normal	Normal
0.2	NA	Results varied	Abnormal[h]
0.4	NA	Results varied	Results varied
4.0	NA	Results varied	Normal
0.15	NA	Abnormal[i]	NA
0.58	NA	Abnormal	NA
2.0–2.5	NA	Normal[j]	NA
0.7[k]	Normal[l]	NA	NA
0.65 (men)	Abnormal[m]	Normal[n]	NA
1.3 (men)	Normal	Normal	NA
0.4 (women)	Normal	Normal	NA
0.8 (women)	Normal	Normal	NA
0.82[o]	50% abnormal[p]	50% abnormal[q]	29% abnormal[r]
1.02	29% abnormal	95% abnormal	100% normal
0.39	Abnormal[s]	Abnormal[t]	NA
0.56	Abnormal	Abnormal	NA
0.84	Normal	Marginal[u]	NA
1.08	Normal	Marginal	NA

continued

TABLE 4-2 Continued

Reference	Subjects	Duration of Study	Baseline Thiamin Intake
Wood et al., 1980	19 men	4–5 wk	NA
Anderson et al., 1986	14 women 14 men	7 d	NA

NOTE: Body weight was maintained in all studies. Thiamin intakes were measured analytically except as noted. **Bold** type is used for intakes that supported normal findings.

[a] NA = not applicable.

[b] Abnormal urinary excretion = < 133 nmol/d (40 μg/d) (no reference values given; judgment of status was based on Foltz et al., 1944).

[c] Abnormal clinical signs = appearance of unspecified manifestations of thiamin deficiency.

[d] Marginal clinical signs = appearance of some manifestations of thiamin deficiency (unspecified).

[e] Abnormal urinary excretion = < 200 nmol/d (60 μg/d) (for males).

[f] Abnormal clinical symptoms = leg pains, muscle tenderness.

[g] Abnormal clinical symptoms = decreased appetite, decreased endurance, increased irritability.

[h] Abnormal metabolism of carbohydrate and abnormal clinical signs (decreased deep reflexes, skin changes, decreased appetite, decreased blood pressure, dull vibratory sense, and edema).

[i] Abnormal urinary excretion = < 200 nmol/d (60 μg/d) (no reference values given by authors; judgment of status was based on Foltz et al., 1944).

[j] Normal urinary excretion = ≥ 67 nmol/d (20 μg/d) thiamin.

(1970), greater weight was given to the well-controlled studies of Sauberlich et al. (1979). With the assumption of a curvilinear relationship with increasing intake, it is concluded that the EAR for thiamin is 1.0 mg/day for men and 0.9 mg/day for women, which represents about a 10 percent decrease for women based on body size and energy needs.

EAR for Men	**19–30 years**	**1.0 mg/day of thiamin**
	31–50 years	**1.0 mg/day of thiamin**

Thiamin Intake During Repletion or Maintenance (mg/d)	Erythrocyte Transketolase Activity	Urinary Excretion of Thiamin	Other
0.45	Abnormal[v]	Abnormal[v]	Normal[w]
5.45	Normal	Normal	Normal
0.97[x]	Abnormal[y]	NA	NA
1.13	Abnormal	NA	NA
1.24	Normal	NA	NA
1.50	Normal	NA	NA

[k] Estimated average intake (0.42 mg/1,000 kcal × 1,745 kcal/d).

[l] Normal erythrocyte transketolase activity (ETKA) was determined by authors from a regression plot.

[m] Abnormal ETKA = > 15% thiamin pyrophosphate (TPP) effect (no reference values given by authors; judgment of status was based on Brin, 1970).

[n] Normal urinary excretion = > 90 nmol/g (27 μg/g) creatinine (no reference values given by authors; judgment of status was based on Schrijver, 1991).

[o] Intake was determined by 3-d dietary recall.

[p] Abnormal ETKA = ≥ 15% thiamin diphosphate effect.

[q] Abnormal urinary excretion = < 500 nmol/g (150 μg/g) creatinine.

[r] Abnormal erythrocyte thiamin = < 270 nmol/L (8 μg/100 mL) erythrocytes.

[s] Abnormal ETKA = ≥ 25% TPP effect.

[t] Abnormal urinary excretion = < 90 nmol/g (27 μg/g) creatinine.

[u] Marginal urinary excretion = 90–217 nmol/g (27–65 μg/g) creatinine.

[v] Abnormal ETKA and urinary excretion: based on the combination of % TPP effect (14–35%) and urinary excretion (< 90 nmol/g [27 μg/g] creatinine).

[w] Normal clinical signs (assessment based on subjective ratings, clinical examinations, psychological assessment, work performance, and neurophysiological assessment).

[x] Intake was determined by 7-d dietary recall questionnaires.

[y] Abnormal ETKA = > 15% TPP effect.

EAR for Women	**19–30 years**	**0.9 mg/day of thiamin**
	31–50 years	**0.9 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Men	**19–30 years**	**1.2 mg/day of thiamin**
	31–50 years	**1.2 mg/day of thiamin**
RDA for Women	**19–30 years**	**1.1 mg/day of thiamin**
	31–50 years	**1.1 mg/day of thiamin**

Adults Ages 51 Years and Older

Evidence Considered in Estimating the Average Requirement

Several studies of the thiamin status of the elderly have been conducted but provide little direct information on which to base nutrient requirements. Laboratory indicators of status suggest that a substantial percentage (20 to 30 percent) of the population has values suggestive of deficiency, but reported intake is not correlated with the laboratory results. Nichols and Basu (1994) investigated the relationship between thiamin intake and the thiamin pyrophosphate (TPP) effect in a group of 60 randomly selected, free-living elderly men and women in Alberta, Canada, aged 65 to 74 years. Thiamin intake estimated from three nonconsecutive food records was not significantly correlated with the TPP effect. In this study, only 57 percent of the subjects were described as having adequate thiamin status (TPP effect of less than 14 percent) even though the reported mean thiamin intake was 1.7 ± 0.12 mg (standard error)/day for men and 1.4 ± 0.01 mg/day for women.

O'Rourke and coworkers (1990) reported a lower TPP effect for 10 healthy elderly individuals (aged 70 to 82 years) than for 13 institutionalized elderly (aged 67 to 92 years) who were apparently free of significant gastrointestinal, hepatic, or renal disease. No differences were found in erythrocyte transketolase activity or erythrocyte thiamin content. The investigators did not report on relationships between thiamin intake and the indicators of status.

In a study of 75 elderly Finnish women and men (aged 50 to 94 years), some of whom were institutionalized, slightly over 20 percent were described as having marginal thiamin deficiency defined as greater than 15 percent TPP (Pekkarinen et al., 1974). The mean intake of thiamin was much lower than in the Nichols and Basu (1994) study mentioned above and it varied by group, ranging from 0.46 to 0.79 mg/day in women and from 0.60 to 0.84 mg/day in men. The enzyme activity of the erythrocytes was not significantly correlated with thiamin intake as determined by thiochrome analysis of collected food samples.

Similarly, Hoorn and colleagues (1975) reported that 23 percent

of 153 geriatric patients aged 65 to 93 years were deficient in thiamin as determined by a transketolase activation coefficient greater than 1.27. Status became normal in all patients after the administration of 20 mg of thiamin daily for 12 days. No dietary information was provided.

A depletion-repletion study of 10 active, healthy elderly women (aged 52 to 72 years, 9 of whom were 63 years or older) measured urinary thiamin excretion after various thiamin intakes (Oldham, 1962). Eight young women aged 18 to 21 years were also studied. On a thiamin intake of less than 0.40 mg/day, the urinary thiamin excretion decreased more quickly for the older than for the younger women. By day 11 or 12, the thiamin excretion of the older women averaged only 0.153 μmol/day (0.05 μg/day), and they complained of fatigue, headaches, and irritability and canceled social engagements. Comparable results were not seen for the younger women until day 19 or 20. When thiamin intake was increased, the older women's urinary thiamin excretion did not increase as quickly as did that of the younger women. The authors concluded that the thiamin requirement of elderly women is higher than that of young women and that the ratio of thiamin to energy must be higher, but the highest thiamin intake level tested, 0.81 mg/day, showed a very wide range of urinary thiamin excretion, especially after 6 days at this intake.

In a randomized, double-blind treatment trial of either 10 mg of thiamin or placebo (Wilkinson et al., 1997), treated subjects who had low TPP concentrations twice when measured before randomization were reported to experience subjective benefits (improved quality of life) and lower blood pressure and weight; those with only one low TPP value prior to randomization did not benefit from treatment.

Although there are some data to suggest that requirements might be somewhat higher in the elderly than in younger adults (e.g., Oldham, 1962), there is also a concomitant decreased energy utilization that may offset this. Further study of this question needs to be conducted. Thus the EAR is assumed to be the same for elderly and younger adults.

Thiamin EAR and RDA Summary, Ages 51 Years and Older

The EAR for thiamin for adults ages 50 and older is set at the same level as for younger adults—1.0 mg/day for men and 0.9 mg/day for women.

EAR for Men	**51–70 years**	**1.0 mg/day of thiamin**
	> 70 years	**1.0 mg/day of thiamin**
EAR for Women	**51–70 years**	**0.9 mg/day of thiamin**
	> 70 years	**0.9 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Men	**51–70 years**	**1.2 mg/day of thiamin**
	> 70 years	**1.2 mg/day of thiamin**
RDA for Women	**51–70 years**	**1.1 mg/day of thiamin**
	> 70 years	**1.1 mg/day of thiamin**

Pregnancy

Method Used to Estimate the Average Requirement

The few studies of the thiamin need of pregnant women focus mainly on single indicators of status, usually without reference to dietary intake. For example, one measurement of transketolase activity was made in each of 556 pregnant German women at various stages of gestation (Heller et al., 1974). The mean activation coefficient was 1.13 whereas that of a reference group of 300 blood donors was 1.05; the cutoff value of normal activation coefficients, derived from data on nonpregnant adults, was 1.20. Twenty-six percent of the women with uncomplicated pregnancies and 21 percent of those with complications had activation coefficients above the cutoff and were classified as abnormal.

Regardless of the nutritional status of the mother, erythrocyte transketolase activity was higher in cord blood than in maternal blood (Tripathy, 1968). Similarly, the free thiamin concentration was higher in cord blood (Slobody et al., 1949). Transketolase activity in cord blood tended to be proportional to that in maternal blood and higher in the blood of pregnant than of nonpregnant women (Tripathy, 1968). In 103 pregnant Malaysian women whose staple diet was rice, 36 percent had a TPP effect greater than 25

percent—a larger percentage than was found for males and nonpregnant women (Chong and Ho, 1970).

Oldham and coworkers (1950) found a very strong correlation ($r = 0.98$) between total thiamin intake and excretion but no consistent decrease in thiamin excretion or in the percentage of a test dose excreted over the course of pregnancy. These investigators compared their results with those from studies of nonpregnant women of comparable ages (Daum et al., 1948; Hathaway and Strom, 1946; Oldham et al., 1946) and found that the pregnant women excreted two to three times as much thiamin as did the nonpregnant women on similar intakes (estimated at less than 1 mg) whereas their excretion of a test dose was similar. In contrast, Toverud (1940) observed no or minimal excretion of thiamin in the urine normally or after a load test in 46 percent of 114 pregnant women. Lockhart and coworkers (1943) reported that approximately three times as much thiamin, as obtained from both supplements and diet, was needed by 16 pregnant women to achieve the urinary excretion peak in the tenth lunar month as was needed by a group of nonpregnant women.

Thiamin EAR and RDA Summary, Pregnancy

For pregnancy the requirement is increased by about 30 percent based on increased growth in maternal and fetal compartments (approximately 20 percent) and a small increase in energy utilization (about 10 percent). This results in an additional requirement for pregnancy of $0.27 \cong 0.3$ mg/day of thiamin. Data from the studies cited above are equivocal about the effects of pregnancy on thiamin requirements and thus are not useful in refining this estimate. Adding 0.3 to the EAR of 0.9 mg for nonpregnant, nonlactating women gives an EAR for the second and third trimesters of pregnancy of 1.2 mg. No adjustment is made for the woman's age.

EAR for Pregnancy	**14–18 years**	**1.2 mg/day of thiamin**
	19–30 years	**1.2 mg/day of thiamin**
	31–50 years	**1.2 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Pregnancy	**14–18 years**	**1.4 mg/day of thiamin**
	19–30 years	**1.4 mg/day of thiamin**
	31–50 years	**1.4 mg/day of thiamin**

Lactation

Method Used to Estimate the Average Requirement

For lactating women it is assumed that 0.16 mg of thiamin is transferred in their milk each day when daily milk production is 0.78 L (see "Ages 0 through 6 Months"). To estimate the average thiamin requirement of lactating women, an additional 0.1 mg of thiamin is added to the EAR (0.9 mg/day) for the nonpregnant, nonlactating woman to cover the energy cost of milk production. Thus, the EAR for thiamin for the lactating woman is

$$0.9 + 0.16 + 0.1 = 1.16 \cong 1.2 \text{ mg/day of thiamin.}$$

Women who are breastfeeding older infants who are eating solid foods might need slightly less thiamin because of a lower volume of milk production.

Thiamin EAR and RDA Summary, Lactation

EAR for Lactation	**14–18 years**	**1.2 mg/day of thiamin**
	19–30 years	**1.2 mg/day of thiamin**
	31–50 years	**1.2 mg/day of thiamin**

The RDA for thiamin is set by assuming a coefficient of variation (CV) of 10 percent (see Chapter 1) because information is not available on the standard deviation of the requirement for thiamin; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for thiamin the RDA is 120 percent of the EAR).

RDA for Lactation	**14–18 years**	**1.4 mg/day of thiamin**
	19–30 years	**1.4 mg/day of thiamin**
	31–50 years	**1.4 mg/day of thiamin**

Special Considerations

Persons who may have increased needs for thiamin include those being treated with hemodialysis or peritoneal dialysis, individuals with malabsorption syndrome, women carrying more than one fetus, and lactating women who are nursing more than one infant.

INTAKE OF THIAMIN

Food Sources

Data obtained from the 1995 Continuing Survey of Food Intakes by Individuals indicate that the greatest contribution to thiamin intake of the U.S. adult population comes from the following enriched, fortified, or whole-grain products: bread and bread products, mixed foods whose main ingredient is grain, and ready-to-eat cereals (Table 4-3). Small differences are seen in the contributions of various foods to the overall thiamin intake of men and women. Other sources include pork and ham products and cereals and meat substitutes fortified with vitamins.

Dietary Intake

Data from nationally representative surveys during the past decade (Appendixes G and H) indicate that the median daily intake of thiamin in the United States by young men was approximately 2 mg and the median intake by young women was approximately 1.2 mg daily. For all life stage and gender groups except lactating females, fewer than 5 percent of the individuals had intakes that were lower than the Estimated Average Requirement (EAR). Five to 10 percent of lactating females had intakes lower than the EAR. Results from Canadian surveys indicate that thiamin intakes in two Canadian provinces were slightly lower than U.S. intakes for both men and women (Appendix I).

The Boston Nutritional Status Survey (Appendix F) indicates that this relatively advantaged group of people over age 60 had a median thiamin intake of 1.4 mg/day for men and 1.1 mg/day for women.

Intake from Supplements

Information from the Boston Nutritional Status Survey conducted on the use of thiamin supplements by a free-living elderly population is given in Appendix F. For those taking supplements, the fifti-

TABLE 4-3 Food Groups Providing Thiamin in the Diets of U.S. Men and Women Aged 19 Years and Older, CSFII, 1995[a]

	Contribution to Total Thiamin Intake[b] (%)		Foods Within the Group that Provide at Least 0.3 mg of Thiamin[c] per Serving	
Food Group	Men	Women	0.3–0.6 mg	> 0.6 mg
Food groups providing at least 5% of total thiamin intake				
Bread and bread products	17.1	17.7	—	—
Mixed foods, main ingredient is grain	9.6	8.1	NA[d]	NA
Ready-to-eat cereals	9.3	11.8	Moderately fortified	Highly fortified
Mixed foods[e]	9.1	6.5	NA	NA
Pasta, rice, and cooked cereals	6.7	7.2	Egg noodles, spinach noodles	Fortified oatmeal
Processed meats[f]	5.8	4.1	Pork sausage	—
Pork	5.6	4.9	—	Pork and ham
Thiamin from other food groups				
Finfish	0.9	1.5	Pompano, fresh tuna, catfish, and trout	—
Soy-based supplements and meal replacements	0.7	0.2	Soy milk	Soy-based meat substitutes
Seeds	0.1	0.3	Sunflower seeds	—

NOTE: Most of the grain products are enriched, whole grain, or fortified.

[a] CSFII = Continuing Survey of Food Intakes by Individuals.

[b] Contribution to total intake reflects both the concentration of the nutrient in the food and the amount of the food consumed. It refers to the percentage contribution to the American diet for both men and women, based on 1995 CSFII data.

[c] 0.3 mg = 20% of the Recommended Daily Intake (1.5 mg) of thiamin—a value set by the Food and Drug Administration.

[d] NA = not applicable. Mixed foods were not considered for this table.

[e] Includes sandwiches and other foods with meat, poultry, or fish as the main ingredient.

[f] Includes frankfurters, sausages, lunch meats, and meat spreads.

SOURCE: Unpublished data from the Food Surveys Research Group, Agricultural Research Service, U.S. Department of Agriculture, 1997.

eth percentile of supplemental thiamin intake was 2.4 mg for men and 3.2 mg for women. Approximately 27 percent of adults surveyed took a thiamin-containing supplement in 1986 (Moss et al., 1989).

TOLERABLE UPPER INTAKE LEVELS

Hazard Identification

Adverse Effects

There are no reports available of adverse effects from consumption of excess thiamin by ingestion of food and supplements. Because the data are inadequate for a quantitative risk assessment, no Tolerable Upper Intake Level (UL) can be derived for thiamin. Supplements that contain up to 50 mg/day of thiamin are widely available without prescription, but the possible occurrence of adverse effects resulting from this level or more of intake appears not to have been studied systematically. The limited evidence of adverse effects after large intakes of thiamin is summarized here.

Anaphylaxis. There have been occasional reports of serious and even fatal responses to the parenteral administration of thiamin (Stephen et al., 1992). The clinical characteristics have strongly suggested an anaphylactic reaction. Symptoms associated with thiamin-induced anaphylaxis include anxiety, pruritus, respiratory distress, nausea, abdominal pain, and shock, sometimes progressing to death (Laws, 1941; Leitner, 1943; Reingold and Webb, 1946; Schiff, 1941; Stein and Morgenstern, 1944; Stiles, 1941).

Allergic Sensitivity and Pruritus. Royer-Morrot and colleagues (1992) reported one case of pruritus after an intake of 500 mg/day of thiamin intramuscularly. Another study (Wrenn et al., 1989), which involved intravenous administration of 100 mg of thiamin hydrochloride to 989 patients, reported a burning effect at the injection site in 11 patients and pruritus in 1 patient. No reports of pruritus after thiamin ingestion were found. Because pruritus was only observed with parenteral administration and at a dosage well above the maximum that can be absorbed, it is irrelevant for setting a UL. The finding of Wrenn and coworkers (1989) supports the conclusion that even intravenous administration of high doses of thiamin is relatively safe.

The apparent lack of toxicity of supplemental thiamin may be

explained by the rapid decline in absorption that occurs at intakes above 5 mg (Hayes and Hegsted, 1973; SCOGS/LSRO, 1978) and the rapid urinary excretion of thiamin (Davis et al., 1984; McAlpine and Hills, 1941; Najjar and Holt, 1940).

Dose-Response Assessment

In the absence of known toxic effects by ingestion, a lowest-observed-adverse-effect level (LOAEL) and an associated no-observed-adverse-effect level (NOAEL) cannot be determined. Supplements that contain up to 50 mg/day of thiamin are widely available without prescription, but effects of this level or more of intake do not appear to have been studied systematically.

Intake Assessment

Although no UL can be set for thiamin, an exposure assessment is provided here for possible future use. Based on data from the Third National Health and Nutrition Examination Survey, the highest mean intake of thiamin from diet and supplements for any life stage or gender group was reported for men aged 31 through 50 years: 6.7 mg/day. The highest reported intake at the ninety-fifth percentile was 11.0 mg/day in women aged 51 years and older (see Appendix H).

Risk Characterization

Although no adverse effects have been associated with excess intake of thiamin from food or supplements, this does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of thiamin intake are extremely limited, caution may be warranted.

RESEARCH RECOMMENDATIONS FOR THIAMIN

Priority should be given to studies useful for setting Estimated Average Requirements (EARs) for thiamin for children, adolescents, pregnant and lactating women, and the elderly. Future studies should be designed around the EAR paradigm, use graded levels of thiamin intake with clearly defined cutoff values for clinical adequacy and inadequacy, and be conducted for a sufficient duration. To do this, close attention should be given to the identification of indicators on which to base thiamin requirements.

If studies are designed to test high doses of thiamin for possible beneficial effects, the design should also provide for the careful investigation of possible adverse effects.

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