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Nutrient Reference Values for Australia and New Zealand
Including Recommended Dietary Intakes

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VITAMIN B₁₂

BACKGROUND

Vitamin B₁₂ is the generic descriptor for those corrinoid compounds exhibiting qualitatively the biological activity of cyanocobalamin. The main cobalamins with physiological action are hydroxycobalamin, methylcobalamin and deoxyadenosylcobalamin. Vitamin B₁₂ is required for the synthesis of fatty acids in myelin and, in conjunction with folate, for DNA synthesis. Adequate intake of vitamin B₁₂ is essential for normal blood function and neurological function. It can be stored in the liver for many years.

Vitamin B₁₂ can be converted to either of the two cobalamin coenzymes that are active in humans; methylcobalamin and 5-deoxyadenosylcobalamin. Vitamin B₁₂ is a cofactor for the enzymes methionine synthase and L-methylmalonyl-CoA mutase and is involved in the conversion of homocysteine to methionine and of L-methylmalonyl-coenzyme A (CoA) to succinyl-CoA. In vitamin B₁₂ deficiency, folate may accumulate in serum as a result of slowing of the vitamin B₁₂-dependent methyltransferase.

Whilst there are some plant-based sources of vitamin B₁₂, such as certain algae and plants exposed to bacterial action or contaminated by soil or insects, humans obtain almost all of their vitamin B₁₂ from animal foods. About 25% of vitamin B₁₂ comes from red meats (Baghurst et al 2000). For adults and children, about 30% and 50%, respectively, is from milk and dairy products (Cobiac et al 1999).

Absorption of vitamin B₁₂ is now known to be more complex than was once thought. In foods, methyl-, deoxyadenosyl-, or hydroxocobalamin are bound to enzymes in meat and other animal foods. The cobalamin is released by the action of acid and pepsin that digest the binding protein in the (normal) stomach. The freed cobalamin forms a stable complex with R binder, a glycoprotein secreted in saliva or by the stomach. Meanwhile, intrinsic factor (IF), a 50 kDa glycoprotein that binds cobalamin, is secreted after a meal by the parietal cells of the stomach. However, the binding of cobalamin to IF does not take place in the stomach as was once thought because its affinity is very low at acid pH.

The R binders are partly degraded in the duodenum by pancreatic proteases. The cobalamin then binds IF with high affinity in the more alkaline environment. Unlike R binders, IF is not digested by pancreatic enzymes. Vitamin B₁₂ from the bile duct can also combine with IF, forming an enterohepatic cycle. The vitamin B₁₂-IF complex then passes unchanged down the small intestine and is absorbed in the terminal ileum by endocytosis after attachment to a specific 460 kDa IF membrane receptor. The receptor only binds vitamin B₁₂ that is attached to IF and does not bind vitamin B₁₂ analogues.

Vitamin B₁₂ absorption increases with increasing intake (Adams et al 1971, Chanarin 1979). It is absorbed at varying rates from different foods ranging from 11% from liver, 24–40% from eggs and trout, to more than 60% from mutton and chicken (Doscherholmen et al 1975, 1978, 1981, Heyssel et al 1966). The low absorption rate from liver probably relates to the liver's very high content of B₁₂. No studies have been reported on red meat, pork or dairy foods or fish other than trout, so a conservative adjustment for bioavailability of 50% for healthy adults with normal gastric function was assumed in developing the intake requirements. If people consumed large amounts of foods naturally rich in vitamin B₁₂, the absorption rate would be lower.

Vitamin B₁₂ added to foods (eg beverages, meat analogues or soy milks) in crystalline form has a similar absorption rate if added in low amounts (<5 µg per dose), but very low absorption (1% or less) if added at 500 µg per dose or above (Berlin et al 1968, Heyssel et al 1996). Excretion of vitamin B₁₂ is generally through the faeces and is proportional to body stores (Adams 1970, Heinrich 1964, Mollin & Ross 1952). Other losses occur through the skin and through metabolic reactions.

Requirements for vitamin B₁₂ can be affected by age, although not all studies confirm this (van Asselt et al 1996). The age effect may act through the influence of increasing levels of atrophic gastritis (Krasinski et al 1986) or reduced gastric acidity (Scarlett et al 1992). Rates of atrophic gastritis in the elderly ranging from 10-30% have been reported in Australia (Andrews et al 1967), the US (Hurwitz et al 1997, Krasinski et al 1986) and Scandinavia (Johnsen et al 1991).

Under utilisation of vitamin B₁₂ may occur in those with genetic defects including deletions or defects in MMA-CoA mutase, transcobalamin II or enzymes in the cobalamin adenosylation pathway.

Vitamin B₁₂ deficiency can produce haematological, neurological or gut symptoms. The haematological effects are indistinguishable from folate deficiency. They include a range of effects generally associated with anaemia such as skin pallor, lowered energy and exercise tolerance, fatigue, shortness of breath and palpitations. The underlying problem is interference with DNA synthesis leading to production of abnormally large erythrocytes.

Neurological complications are present in about 75–90% of people with frank deficiency. These complications appear to be inversely related to the occurrence of the haematological symptoms (Healton et al 1991, Savage et al 1994). They include sensory disturbances in the extremities, motor disturbance and cognitive changes from memory loss to dementia, with or without mood change. There may also be visual disturbances, impotency and impaired bowel and bladder control. A study by Louwman et al (2000) indicated that cobalamin deficiency in the absence of haematological signs may also affect cognitive function in adolescence.

The indicators that are available for estimating requirements for vitamin B₁₂ include haematological response as well as measures of serum or plasma vitamin B₁₂, MMA, homocysteine, formiminoglutamic acid, propionate and methylcitrate and holo-transcobalamin II.

Haematological responses that have been assessed include increases in haemoglobin, haematocrit and erythrocyte count or decreases in MCV or an optimal rise in reticulocyte numbers. Of these, MCV has limited use because of the 120 days needed to see change, and whilst erythrocyte, haemoglobin and haematocrit are robust they are slow to change. However, reticulocyte count is useful as increases in response to diet are apparent within 48 hours and reach a peak in 5–8 days.

Serum or plasma vitamin B₁₂ reflects both intake and stores but acceptable levels can be maintained for some time after deficiency occurs because of compensatory release of vitamin B₁₂ from tissues. Low levels would, however, represent long-term deficiency or chronic low intakes. MMA exhibits a four-fold range in the normal population but rises when the supply of vitamin B₁₂ is low or when absorption is affected (Joosten et al 1996). Elevated MMA levels can be reduced by vitamin B₁₂ administration (Joosten et al 1993, Naurath et al 1995, Norman & Morrison 1993, Pennypacker et al 1992).

As the presence of elevated MMA represents a vitamin B₁₂-specific change, MMA is the preferred indicator of vitamin B₁₂ status. However, there are not sufficient data available to use MMA levels to set dietary recommendations. Homocysteine concentration does change in response to vitamin B₁₂ status but it is not specific to vitamin B₁₂, responding also to folate or vitamin B₆ status or both, and formiminoglutamic acid also changes with folate status. Propionate and methylcitrate both respond to changes in vitamin B₁₂ status (Allen et al 1993), however they offer no advantages over MMA. Measures of holotranscobalamin II are insufficiently robust to allow the assessment of requirements.

RECOMMENDATIONS BY LIFE STAGE AND GENDER

<i>Infants</i>	AI	Vitamin B₁₂
0–6 months	0.4 µg/day	
7–12 months	0.5 µg/day	

Rationale: The AI for 0–6 months is based on the Vitamin B₁₂ intake of infants fed breast milk. The AI was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of vitamin B₁₂ in breast milk, and rounding (FNB:IOM 1998). Reported values of breast milk concentration vary widely, partly because of differences in analytical methods and partly because of variation in maternal vitamin B₁₂ status and current intake. Median values are substantially lower than mean values. In a study of 9 well-fed Brazilian mothers whose infants were exclusively breastfed, the average concentration in breast milk was 0.42 µg/L at 2 months and 0.34 µg/L at 3 months (Trugo &

Sardinha 1994). The 2-month value was chosen to ensure adequate intake and multiplied by the daily milk volume (0.42 µg/L x 0.78 L/day = 0.33 µg/day) and rounded up to give the AI of 0.4 µg. As there are few data for the vitamin B₁₂ content of weaning diets, the AI for 7–12 months was estimated by extrapolating up from the 0–6 month AI. This was cross-checked by extrapolating from the adult EAR and adjusting for the expected variance to estimate a recommended intake. The former estimate gave a value of 0.5 µg/day after rounding up and the latter, 0.6 µg/day. The AI was set at 0.5 µg/day.

Note: To ensure adequate vitamin B₁₂ status in their infants, and prevent severe outcomes including cognitive impairment or even coma in the infant, vegan mothers should supplement their diets with vitamin B₁₂ at the RDI level throughout pregnancy and lactation on the basis of evidence that stores in infants of vegan mothers at birth are low and the milk may supply only very small amounts (Specker et al 1990). Soy formula used during weaning needs to be fortified with vitamin B₁₂ to an equivalent level. If the mother is not supplemented in pregnancy and lactation and the child is breast fed, then the infant will need supplements from birth.

<i>Children & adolescents</i>	EAR	RDI	Vitamin B₁₂
All			
1–3 yr	0.7 µg/day	0.9 µg/day	
4–8 yr	1.0 µg/day	1.2 µg/day	
Boys			
9–13 yr	1.5 µg/day	1.8 µg/day	
14–18 yr	2.0 µg/day	2.4 µg/day	
Girls			
9–13 yr	1.5 µg/day	1.8 µg/day	
14–18 yr	2.0 µg/day	2.4 µg/day	

Rationale: There are few data on children or adolescents on which to base the EAR so the EAR was set by extrapolation from adult data adjusting for body weight and with reference to growth needs, and rounding up (FNB:IOM 1998). In the absence of information on the standard deviation of the requirement, the RDI was set assuming a CV of 10% for the EAR. Note that vegan children will need supplementation.

<i>Adults</i>	EAR	RDI	Vitamin B₁₂
Men			
19-30 yr	2.0 µg/day	2.4 µg/day	
31-50 yr	2.0 µg/day	2.4 µg/day	
51-70 yr	2.0 µg/day	2.4 µg/day	
>70 yr	2.0 µg/day	2.4 µg/day	
Women			
19-30 yr	2.0 µg/day	2.4 µg/day	
31-50 yr	2.0 µg/day	2.4 µg/day	
51-70 yr	2.0 µg/day	2.4 µg/day	
>70 yr	2.0 µg/day	2.4 µg/day	

Rationale: The EAR for adults was set on the basis of haematological evidence and serum vitamin B₁₂ levels (FNB:IOM 1998). Sufficient data were not available to discern differences in requirements for men and women. In the absence of information on the standard deviation of the requirement, the RDI was set assuming a CV of 10% for the EAR. Note that strict vegans will need supplementation with vitamin B₁₂.

Note: The natural vitamin B₁₂ in foods may be less bioavailable to the substantial number of older adults who have atrophic gastritis with low stomach acid secretion. People with this condition may require higher intakes of vitamin B₁₂-rich foods, vitamin B₁₂-fortified foods or supplements.

Pregnancy	EAR	RDI	Vitamin B₁₂
14–18 yr	2.2 µg/day	2.6 µg/day	
19–30 yr	2.2 µg/day	2.6 µg/day	
31–50 yr	2.2 µg/day	2.6 µg/day	

Rationale: The EAR was set on the basis of the maternal EAR plus an allowance for fetal and placental needs. Fetal accumulation averages 0.1–0.2 µg/day (Baker et al 1962, Loria et al 1977, Vaz Pinto et al 1975) but placental accumulation is only 14 ng/L (Muir & Landon 1985). An additional 0.2 µg/day was therefore added to the maternal requirement and the RDI was then derived assuming a CV of 10% for the EAR. Vegan mothers will need supplementation throughout pregnancy and during lactation in sufficient amounts to ensure adequate supplies for themselves and their child.

Lactation	EAR	RDI	Vitamin B₁₂
14–18 yr	2.4 µg/day	2.8 µg/day	
19–30 yr	2.4 µg/day	2.8 µg/day	
31–50 yr	2.4 µg/day	2.8 µg/day	

Rationale: The EAR for lactation was set by adding the average amount secreted in milk (0.33 µg/day) to the maternal EAR, and rounding up. The RDI was set assuming a CV of 10% for the EAR. Vegan mothers will need supplementation in lactation in sufficient amounts to ensure adequate supplies for themselves and their child.

UPPER LEVEL OF INTAKE - VITAMIN B₁₂

There are insufficient data to allow setting of a UL.

There is no evidence that the current levels of intake from foods and supplements represent a health risk. No adverse effects have been associated with excess vitamin B₁₂ intake from food or supplements in healthy individuals. There is weak evidence from animal studies that vitamin B₁₂ may potentiate the effects of carcinogenic chemicals (Day et al 1950, Georgadze 1960, Kalnev et al 1977, Ostryanina 1971) but other studies contradict this (Rogers 1975). The apparent lack of toxicity could relate to the body's ability to decrease absorption in response to high intakes. As there are no dose-response data, no UL can be set.

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