The following is an extract from:

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

ENDORSED BY THE NHMRC ON 9 SEPTEMBER 2005

ISBN Print 1864962372
ISBN Online 1864962437

The Nutrient Reference Values (NRVs) was a joint initiative of the Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH). The NHMRC would like to thank the New Zealand MoH for allowing the use of the NRV material in the development of this website.

NHMRC publications contact:
Email: nhmrc.publications@nhmrc.gov.au
Internet: http://www.nhmrc.gov.au
Free Call: 1800 020 103 ext 9520

RIBOFLAVIN

BACKGROUND

Riboflavin is a water-soluble vitamin. The bioactive forms of riboflavin are the oxidised and reduced forms of flavin adenine dinucleotide (FAD and $FADH_2$, respectively) and flavin mononucleotide (FMN and $FMNH_2$, respectively) (FNB:IOM 1998, McCormick 2000, Thurnham 2000). They function as co-enzymes for key reactions in the catabolism of fuel molecules (eg β-oxidation of fatty acids, Krebs cycle), and in certain biosynthetic pathways (eg fatty acid synthesis). Riboflavin and its derivatives are important for the body's handling of some other nutrients including conversion of vitamin B-6 to its bioactive form, pyridoxal phosphate; conversion of tryptophan to niacin and conversion of methylenetet rahydrofolate (MTHF) to methylTHF by the enzyme methyleneTHF reductase (MTHFR).

As methylTHF is essential for the conversion of homocysteine to methionine, riboflavin deficiency can result in raised plasma levels of homocysteine that are associated with increased cardiovascular risk. A cross-sectional study (McNulty et al 2002) suggested that this association is much more likely to occur in individuals with the TT genetic variant of MTHFR (ie homozygous for the C677T polymorphism), which is found in about 12% of humans, than those with the CT or CC variants. Powers (2003) also noted that riboflavin deficiency is often associated with anaemia, which may result from problems in the body's handling of iron.

The metabolism of riboflavin is tightly controlled and depends on the riboflavin status of the individual (Lee & McCormick 1983). Riboflavin is converted to coenzymes mostly in the small intestine, liver, heart and kidney (Brown 1990, Darby 1981). Surplus riboflavin is excreted in urine, either as riboflavin itself (about two-thirds of total excretion) or as a range of metabolites. In deficiency, only small amounts are excreted.

Most of the riboflavin in our foods occurs as the nucleotides FAD/$FADH_2$ and FMN/$FMNH_2$ in a complex of food protein (Merrill et al 1981, Nicholalds 1981). This is released as free riboflavin by digestive enzymes in the small intestine and absorbed into the bloodstream. The major sources are milk and milk products and fortified breads and cereals. The bioavailability of riboflavin is high, probably about 95% (Zempleni et al 1996), but our capacity to absorb riboflavin from the small intestine is only moderate.

The classic disease of riboflavin deficiency is ariboflavinosis, which manifests in growth disturbances, seborrhaeic dermatitis, inflammation of the oral mucosa and tongue, cracks at the corner of the mouth and normocytic anaemia (Wilson 1983).

A range of indicators has been used to assess riboflavin status. These include clinical assessment of the classic physical symptoms of deficiency indicating severe deficiency, urinary excretion of riboflavin, erythrocyte flavin levels and determination of the erythrocyte glutathione reductase activity coefficient (EGRAC) in which erythrocyte glutathione reductase is assayed in the presence and absence of added FAD to establish an in vitro activity coefficient. This value provides an indirect indicator of cellular FAD levels and, by extrapolation, an indicator of whole body riboflavin status. Unfortunately, different studies have used different reference ranges for EGRAC. All of these methods are reasonably satisfactory indicators (Hustad et al 2002), however erythrocyte flavin has not been widely used.

RECOMMENDATIONS BY LIFE STAGE AND GENDER

Infants	**AI**	**Riboflavin**
0–6 months	**0.3 mg/day**	
7–12 months	**0.4 mg/day**	

***Rationale*:** The AI for 0–6 months was calculated by multiplying together the average intake of breast milk (0.78 L/day) and the average concentration of riboflavin in breast milk (0.35 mg/L) from the studies of Roughead & McCormick (1990) and WHO (1965), and rounding (FNB:IOM 1998). The FNM: IOM found that the AI estimate using intake data for thiamine for 7–12 months were unreasonably high when compared to extrapolation data from either younger infants or adults. The AI for 7–12 months was derived from estimating requirements on a body weight basis from the value for younger infants of 0.35 mg/day and from adults, using a metabolic weight ratio, including consideration for growth (0.35 mg/day) and rounding.

Children & adolescents	**EAR**	**RDI**	**Riboflavin**
All			
1–3 yr	**0.4 mg/day**	**0.5 mg/day**	
4–8 yr	**0.5 mg/day**	**0.6 mg/day**	
Boys			
9–13 yr	**0.8 mg/day**	**0.9 mg/day**	
14–18 yr	**1.1 mg/day**	**1.3 mg/day**	
Girls			
9–13 yr	**0.8 mg/day**	**0.9 mg/day**	
14–18 yr	**0.9 mg/day**	**1.1 mg/day**	

***Rationale*:** As there are limited data specific to these age groups, EARs were derived from the adult recommendations using a metabolic body weight ratio estimate including an allowance for growth. The RDI was set assuming a CV of 10% for the EAR.

Adults	**EAR**	**RDI**	**Riboflavin**
Men			
19–30 yr	**1.1 mg/day**	**1.3 mg/day**	
31–50 yr	**1.1 mg/day**	**1.3 mg/day**	
51–70 yr	**1.1 mg/day**	**1.3 mg/day**	
>70 yr	**1.3 mg/day**	**1.6 mg/day**	
Women			
19–30 yr	**0.9 mg/day**	**1.1 mg/day**	
31–50 yr	**0.9 mg/day**	**1.1 mg/day**	
51–70 yr	**0.9 mg/day**	**1.1 mg/day**	
>70 yr	**1.1 mg/day**	**1.3 mg/day**	

***Rationale*:** The EARs for adults from 19–70 years were based on a series of studies addressing clinical deficiency signs and biochemical markers, including EGRAC, in relation to measured dietary intake (Belko et al 1983, Bessey et al 1956, Boisvert et al 1993, Brewer et al 1946, Davis et al 1946, Horwitt et al 1949, 1950, Keys et al 1944, Kuizon et al 1992, Roe et al 1982, Sebrell et al 1941, Williams et al 1943). The RDI was derived assuming a CV of 10% for the EAR (FNB:IOM 1998).

As energy expenditure decreases with age, it would be expected that the EAR for older people may also decrease. However two studies question this assumption. Boisvert et al (1993) showed that for elderly Guatemalans, normalisation of EGRAC was achieved with 1.3 mg/day riboflavin and that a sharp increase in urinary riboflavin occurred at intakes above 1.0–1.1 mg/day, suggesting that needs were similar to those of younger adults.

A well-controlled UK study of free-living (ie not in residential care) elderly people over 65 years (Madigan et al 1998) showed that in a population where nearly all subjects had intakes above 1.3 mg/day for men and 1.1 mg/day for women, 12% were deficient (>1.4 EGRAC) and a further 33% had low riboflavin status. Thus the EAR for the elderly was set at 1.3 mg/day for men and 1.1 mg/day for elderly women. The RDI was set assuming a CV of 10% for the EAR.

Pregnancy	**EAR**	**RDI**	**Riboflavin**
14–18 yr	**1.2 mg/day**	**1.4 mg/day**	
19–30 yr	**1.2 mg/day**	**1.4 mg/day**	
31–50 yr	**1.2 mg/day**	**1.4 mg/day**	

***Rationale*:** In pregnancy, an additional requirement of 0.3 mg/day is estimated based on increased growth in maternal and fetal tissues and an increase in energy expenditure (FNB:IOM 1998). This added to the requirement for non-pregnant women to give an EAR of 1.2 mg/day. The RDI was set assuming a CV of 10% for the EAR.

Lactation	**EAR**	**RDI**	**Riboflavin**
14–18 yr	**1.3 mg/day**	**1.6 mg/day**	
19–30 yr	**1.3 mg/day**	**1.6 mg/day**	
31–50 yr	**1.3 mg/day**	**1.6 mg/day**	

***Rationale*:** In lactation it is assumed that 0.3 mg/day of riboflavin is transferred into milk. Use of riboflavin for milk production is estimated as 70% (WHO 1965) meaning that 0.4 mg/day is required. This amount is added to the EAR recommended for non-pregnant, non-lactating women and the RDI is set by assuming a CV of 10% for the EAR.

UPPER LEVEL OF INTAKE - RIBOFLAVIN

The upper level of intake cannot be estimated.

No adverse events have been associated with riboflavin consumption as food or supplements so no upper level of intake can be set. Studies using large doses of riboflavin have been undertaken, but they were not designed to assess adverse effects systematically (Schoenen et al 1998, Stripp 1965, Zempleni et al 1996). The only evidence of adverse effects comes from in vitro studies indicating a potential increase in photosensitivity to ultraviolet radiation (Ali et al 1991, Floersheim 1994, Spector et al 1995).

REFERENCES

Ali N, Upreti RK, Srvastava LP, Misra RB, Joshi PC, Kidwai AM. Membrane damaging potential of photosensitized riboflavin. *Indian J Exp Biol* 1991;29:818–22.

Belko AZ, Obarzanek E, Kalkwarf HJ, Rotter MA, Bogusz S, Miller D, Haas JD, Roe DA. Effects of exercise on riboflavin requirements of young women. *Am J Clin Nutr* 1983;37:509–17.

Bessey OA, Horwitt MK, Love RH. Dietary deprivation of riboflavin and blood riboflavin levels in man. *J Nutr* 1956;58:367–83.

Boisvert WA, Mendoze I, Casteñada C, de PortoCarrero L, Solomons NW, Gershoff SN, Russell RM. Riboflavin requirement of healthy elderly humans, and its relationship to macronutrient composition of the diet. *J Nutr* 1993;123:915–25.

Brewer W, Porter T, Ingalls R, Ohlson MA. The urinary excretion of riboflavin by college women. *J Nutr* 1946;32:583–96.

Brown ML. *Present knowledge in nutrition 6th edition.* Washington DC; International Life Sciences Institute – Nutrition Foundation, 1990.

Davis MV, Oldham HG, Roberts LJ. Riboflavin excretions of young women on diets containing varying levels of the B Vitamins. *J Nutr* 1946;32:143–61.

Floersheim GL. Allopurinol indomethacin and riboflavin enhance radiation lethality in mice. *Radiat Res* 1994;139:240–7.

Food and Nutrition Board: Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline.* Washington DC: National Academy Press, 1998.

Horwitt MK, Hills OW, Harvey CC, Liebert E, Steinberg DL. Effects of dietary depletion of riboflavin. *J Nutr* 1949;39:357–73.

Horwitt MK, Harvey CC, Hills OW, Liebert E. Correlation of urinary excretion of riboflavin with dietary intake and symptoms of ariboflavinosis. *J Nutr* 1950;41:247–64.

Hustad S, McKinley MC, McNulty H, Schneede J, Strain JJ, Scott JM, Ueland PM. Riboflavin, flavin mononucleotide and flavin adenine dinucleotide in human plasma and erythrocytes at baseline and after low-dose riboflavin supplementation. *Clin Chem* 2002;48:1571–7.

Keys A, Henschel AF, Mickelsen O, Brozek JM, Crawford JH. Physiological and biochemical functions in normal young men on a diet restricted in riboflavin. *J Nutr* 1944;27:L165–L178.

Kuizon MD, Natera MG, Alberto SP, Perlas LA, Desnacido JA, Avena EM, Tajaon RT, Macapinlac MP. Riboflavin requirement of Filipino women. *Am J Clin Nutr* 1992;46:257–64.

Lee SS, McCormick DB. Effect of riboflavin status on hepatic activities of flavin-metabolizing enzymes in rats. *J Nutr* 1983;113:2274–9.

Madigan SM, Tracey F, McNulty H, Eaton-Evans J, Coulter J, McCartney H, Strain JJ. Riboflavin and vitamin B-6 intakes and status, and biochemical response to riboflavin supplementation, in free-living elderly people. *Am J Clin Nutr* 1998;68:389–95.

McCormick DB. Niacin, riboflavin and thiamin. In: Stipanuk MH ed. *Biochemical and Physiological Aspects of Human Nutrition.* Philadelphia: Saunders, 2000. Pp 458–82.

McNulty H, McKinley MC, Wilson B, McPartlin J, Strain JJ, Weir DG, Scott JM. Impaired functioning of thermolabile methylenetetrahydrofolate reductase is dependent on riboflavin status: implications for riboflavin requirements. *Am J Clin Nutr* 2002;76:436–41.

Merrill AH Jnr, Foltz AT, McCormick DB. Vitamins and cancer. In: Alfin-Slater RB, Kritchevsky D, eds. *Cancer and nutrition.* New York: Plenum, 1981. Pp 261–320.

Nicholalds GE. Riboflavin Symposium in Laboratory Medicine. In: Labbae RF, ed. *Symposium on laboratory assessment of nutritional status.* Clinics in Laboratory Medicine Series. Vol. 1. Philadelphia: WB Saunders, 1981. Pp 685–98.

Powers HJ. Riboflavin (vitamin B-2) and health. *Am J Clin Nutr* 2003;77:1352–60.

Roe DA, Bogusz S, Sheu J, McCormick DB. Factors affecting riboflavin requirements of oral contraceptive users and non-users. *Am J Clin Nutr* 1982;35:495–501.

Roughead ZK, McCormick DB. Flavin composition of human milk. *Am J Clin Nutr* 1990;52:854–7.

Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis: a randomized controlled trial. *Neurology* 1998;50:466–70.

Sebrell WH, Butler RE, Wooley JG, Isbell H. Human riboflavin requirement estimated by urinary excretion of subjects on controlled intake. *Publ Health Rep* 1941;56:510–9.

Spector A, Wang GM, Wang RR, Li WC, Kleiman NJ. A brief photochemically-induced oxidative insult causes irreversible lens damage and cataracts. 2. Mechanism of action. *Exp Eye Res* 1995;60:483–93.

Stripp B. Intestinal absorption of riboflavin by man. *Acta Pharmacol Toxicol* 1965;22: 353–62.

Thurnham DI. Vitamin C and B vitamins: thiamin, riboflavin and niacin. In: Garrow JS, James WPT, Ralph A, eds. *Human Nutrition and Dietetics 10th edn.* Edinburgh, Churchill-Livingstone, 2000. Pp 249–68.

Williams RD, Mason HL, Cusick PL, Wilder RM. Observations on induced riboflavin deficiency and the riboflavin requirements of man. *J Nutr* 1943;25:361–77.

Wilson JA. Disorders of vitamins: deficiency, excess and errors in metabolism. In: Petesdorf RG, Harrison TR, eds. *Harrison's principles of internal medicine, 10th ed.* New York: McGraw-Hill, 1983. Pp 461–70.

World Health Organization. *Nutrition in pregnancy and lactation.* Report of a WHO expert committee. Technical Report Series No. 302. Geneva: World Health Organization, 1965.

Zempleni J, Galloway JR, McCormick DB. Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans. *Am J Clin Nutr* 1996;63:54–66.