Riboflavin

Riboflavin, mg/d		Women	Men	Children		
				2-5 y	6-9 y	10-13 y girls/boys
Recommended intake	RI	1.3	1.7	0.7	1.1	1.2/1.4
Average requirement	AR	1.1	1.4			
Lower intake level	LI	0.8	0.8			
Upper intake level	UL	ND	ND			

Introduction

Riboflavin has its function as precursors for coenzymes, FMN (flavin mononucleotide), FAD (flavin adenin dinucleotide) and covalently bound flavin. These are necessary components of a number of oxidative enzyme systems and participate in the electron transport (Food and Nutrition Board 1998).

Dietary sources and intake

Major sources of riboflavin in the Nordic diets are milk and milk products, meat and meat products. The average dietary intake according to national dietary surveys is in the range of 1.9 – 2.3 mg/10 MJ (see chapter XX Dietary intake in Nordic countries).

Physiology and metabolism

Riboflavin occurs in foods free or as FAD or FMN as a complex with protein. Protein bound riboflavin is hydrolysed to free riboflavin in the gastrointestinal tract and absorbed via a specific transport mechanism (Food and Nutrition Board 1998, Rivlin 1970, Said 2011, SCF 2000). This mechanism is saturated at doses of about 30-50 mg, Absorption rates of free riboflavin are reported to be 50-60 % at doses of 2-25 mg (SCF 2000). Studies on whole foods have shown absorption rates of 60-70 % (Dainty et al. 2007).

Riboflavin is mainly stored in the body as flavoproteins and to a lesser degree as free riboflavin. As a consequence, urinary excretion may be affected by changes in nitrogen balance. The urinary excretion of riboflavin may increase in conditions of negative nitrogen balance and infections, while the opposite may be seen in rapid growth (Sauberlich 1975). No consistent relation has been found between riboflavin requirement, measured by urine excretion or retention, and protein intake in situations of positive protein balance. Riboflavin is also involved in the folate metabolism in that FAD is a co-enzyme for methylenetetrahydrofolate reductase (MTHFR), which influences the metabolism of homocysteine. Low riboflavin status, assessed by erythrocyte gluthathion reductase (EGRAC), has been associated with increased plasma homocysteine levels in subjects with a specific genotype of the MTHFR (McNulty 2002).

Biomarkers of riboflavin status include the activity coefficient of (EGRAC) and urinary excretion of the vitamin (Powers 1999). At habitual intakes urine excretion is proportional to the intake, since the body has a small body pool (SCF 2000). Depletion-repletion studies show that the urinary excretion of riboflavin increases gradually with increasing intakes, with a sharp increase at intakes about 1 mg/d, indicating tissue saturation. The EGRAC represents the degree of stimulation of the enzyme activity in vitro after addition of FAD. A ratio of 1.0 indicates absence of stimulation. There is generally a relation between the activity coefficient and the riboflavin intake, which is most clear at intakes up to about 1 mg/d. Different criteria for normal EGR-activity have been suggested, which may complicate the interpretation of results from studies on riboflavin status (Food and Nutrition Board 1998, 7, 8). EGRAC ratios above 1.3-1.4 have been suggested to indicate deficiency and a ratio 1.0-1.2 indicating adequate status (Food and Nutrition Board 1998).

Although the metabolic effects of riboflavin deficiency are profound, there are only a few clear-cut clinical symptoms. These include various skin changes (angular stomatitis, seborrheic dermatitis) and glossitis. Severe riboflavin depletion has been associated with impaired iron status, anemia and mental disturbances (13). Isolated dietary riboflavin deficiency does usually not occur, but deficiency is normally seen in association with other nutritional deficiencies.

Clinical signs of riboflavin deficiency have been observed in men at intakes of 0.6 mg/d or less, corresponding to 0.06 mg/MJ (0.25 mg/1000 kcal) (Food and Nutrition Board 1998, 9-12). In a long-term study consumption of a diet containing 0.75-0.85 mg/d (0.3-0.4 mg/1000 kcal (4.2 MJ) during up to two years certain clinical symptoms were observed in one man.
Powers et al. (2011) found that supplementation with riboflavin improved some markers of iron status in women with biochemical signs of deficiency based on EGRAC (>1.40). However, significant improvements were seen only in those women with EGRAC ratios above 1.65, indicating that the upper threshold for inadequacy may be too low.

Health effects
Several epidemiological studies have investigated the relationship between intake of riboflavin, and other B-vitamins (folate, vitamin B6 and B12), and various cancers, mainly colorectal and breast cancer. Results from prospective or nested case-control studies published between 2000 and 2012 have found no association (Sharp2008; de Vogel2008; Shrubsole2009; Key2012; Kabat2008; Maruti2009; Basset2012). A few retrospective case-control studies have found an inverse relation (Sun et al. 2012; van den Donk et al. 2005), while others have found no association (Sharp2008; Curtin2011; Ma2009; Bosetti2007; Pelucchi2009). Results studies using biomarkers of riboflavin intake are also inconclusive (Weinstein2008; Johansson2009; Eussen2010a,b; de Vogel2001).

Requirement and recommended intake
In setting dietary reference values previous expert groups have related the riboflavin intake to either energy or protein intake (9,11,12). The US dietary reference intakes are based on absolute intakes (Food and Nutrition Board 1998). Generally, riboflavin metabolism and intake are related to energy and protein intake at normal intake ranges of populations such as the Nordic. However, at low energy intakes (below 8 MJ/d) the requirement expressed per MJ may be higher, while the opposite may be the case at energy intakes well above 12 MJ/d.

In NNR 2004 and 1996, the average requirement (AR) was estimated to 0.12 mg/MJ based on older studies in which riboflavin status was assessed using mainly urinary excretion of riboflavin, to lesser extent on EGRAC. There are limited new scientific data for setting reference values for riboflavin.

Few, generally small, controlled studies in healthy adults in Western populations have assessed effects of graded intakes of riboflavin on EGRAC-ratios (Roe et al. 1982; Belko et al. 1983; Toh et al. 1994) where cut-offs used for adequacy were 1.2-1.25. Recent data indicate that the commonly used threshold for the EGRAC-ratio inadequacy (1.3-1.4) may be too low (Powers et al. 2011).

There is insufficient data to change the reference values from NNR 2004. Thus, a RI of 0.14 mg/MJ is maintained, which applies to both children and adults. This level corresponds to an intake of about 1.6 mg/d for adult men and 1.3 mg/d for adult women with moderate physical activity. However, when planning diets, the riboflavin content should not be lower than 1.2 mg/d, even at energy intake below 8 MJ/d (9). For pregnant and lactating women an extra 0.3 and 0.4 mg/d, respectively, is recommended.

The lower intake level (LI) is estimated to 0.8 mg/d based on earlier depletion-repletion studies.

Upper intake level and toxicity

There are no reports of adverse effects of high riboflavin intakes from dietary sources. The limited studies in which large doses (100-400 mg/d) of supplemental riboflavin have been administered do not indicate any adverse effects (SCF 2000). There are insufficient data to set an UL for riboflavin.

Reasoning behind the recommendation

There is insufficient data to change the reference values from NNR 2004. Thus, a RI of 0.14 mg/MJ is maintained, which applies to both children and adults. This corresponds to an intake of about 1.6 mg/d for adult men and 1.3 mg/d for adult women with moderate physical activity. However, when planning diets, the riboflavin content should not be lower than 1.2 mg/d, even at energy intake below 8 MJ/d (FAO/WHO 1967). For pregnant and lactating women an extra 0.3 and 0.4 mg/d, respectively, is recommended.

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