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Review article

Revised reference values for the intake of thiamin (vitamin B_1), riboflavin (vitamin B_2), and niacin

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ABSTRACT

Background: The nutrition societies of Germany, Austria, and Switzerland are the joint editors of the 'reference values for nutrient intake'. They have revised the reference values for the intake of thiamin, riboflavin, and niacin and published them in February 2015.
Methods: All three vitamins have important functions as part of energy metabolism. Consequently, the reference values for the intake of these vitamins are derived in consideration of the reference values for energy intake (PAL 1.4).
Results: The reference values for infants aged 0 to under 4 months are derived from the nutrient content of breast milk. No data are available regarding thiamin, riboflavin, and niacin requirements for infants aged 4 to under 12 months, children, and adolescents. Therefore, the reference values for these age groups are based on the average requirement for adults and are calculated taking into account the age-based guiding values for energy intake (PAL 1.4) and assuming a coefficient of variation of 10%, due to the variation in requirement within the population. There are no data to suggest that the relationship between thiamin, riboflavin, niacin and energy requirement for pregnant and lactating women is any different from that for women who are not pregnant or not lactating.
Conclusion: Supplemental intake beyond the recommended amounts has no health benefit and is therefore not recommended.

Contents

1. Introduction

The D-A-CH 'reference values for nutrient intake' [1] are jointly issued by the nutrition societies of Germany, Austria, and Switzerland [the abbreviation D-A-CH stands for the initial letters of the common country identification for the countries Germany (D), Austria (A) and

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Switzerland (CH)]. Currently, the 'reference values for nutrient intake' are being revised. Following the revision of the reference values for vitamin D [2], calcium [3], folate [4], energy [5], selenium [6], and vitamin C [7] intake the revised reference values for thiamin, riboflavin, and niacin intake were published in February 2015.

Reference value is a collective term for recommended intake values, estimated values, and guiding values. A recommended intake value, according to its definition, meets the requirement of nearly any person (approximately 98%) of a defined group of healthy people. Estimated values are given when human requirements cannot be determined with desirable accuracy. Guiding values are stated in terms of aids for orientation [1].

The water-soluble B vitamins thiamin, riboflavin, and niacin have important functions as part of energy metabolism. Consequently, the reference values for the intake of these vitamins are derived in consideration of the reference values for energy intake [5].

In foods of animal origin, 95%–98% of *thiamin* is present in phosphorylated form, while thiamin in foods of plant origin is predominantly present as free thiamin [8]. In the human organism, thiamin diphosphate (TDP), also known as thiamin pyrophosphate (TPP), acts as a co-enzyme in important energy metabolism reactions. *Riboflavin* is a precursor of the co-enzymes flavin mononucleotide (FMN; riboflavin phosphate) and flavin adenine dinucleotide (FAD), which are components of oxidases and dehydrogenases [9].

Niacin is a general term for nicotinic acid (pyridine-3-carbonic acid) and nicotinamide (pyridine-3-carboxamide) as well as their derivatives. They are the basis for the formation of the pyridine nucleotides – nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) – that act as co-enzymes[1]. Niacin is present in foods and formed in the human body in the liver from the essential amino acid tryptophan [10].

The niacin concentration in food as well as niacin intake and the reference values are specified in niacin equivalents (1 mg niacin equivalent = 1 mg niacin = 60 mg tryptophan) [11,12]. The amount of niacin equivalents is therefore calculated as niacin (mg) = nicotinamide (mg) + nicotinic acid (mg) + 1/60 tryptophan (mg) [13].

Since there is no evidence of adverse effects in humans, there are no tolerable upper intake levels given for thiamin and riboflavin [14,15]. For niacin, the US–American Institute of Medicine (IOM) defines age-dependent tolerable upper intake levels ranging from 10 mg/day for children up to 35 mg/day for adults [15]. The European Food Safety Authority (EFSA) differentiates between nicotinamide and nicotinic acid since nicotinamide rarely causes adverse effects compared to nicotinic acid in consequence of high intake. The tolerable upper intake levels for adults are 900 mg/day for nicotinamide and 10 mg/day for nicotinic acid [14].

2. Criteria for the assessment of the supply of thiamin, riboflavin, and niacin

Thiamin supply can be determined by measuring the transketolase activity in erythrocytes, which require TDP as a co-enzyme. The measurement of transketolase activity in erythrocytes is a functional parameter that is primarily used to assess thiamin supply [16]. TDP effects of >25% are defined as deficiency and effects between 15% and 25% as marginal deficiency [17].

Further status parameters used for the determination of thiamin supply are determination of TDP concentration in erythrocytes and measurement of thiamin excretion in urine [16,18].

Determination of erythrocytic TDP concentration is a sensitive detection method yielding similar results to the measurement of transketolase activity. A fall in TDP concentration in erythrocytes below 120 nmol/l indicates deficiency [16,18]. With regard to the measurement of the 24-hour urinary excretion of thiamin, excretion levels between 27 μg and 65 μg are defined as marginal deficiency and of <27 μg as deficiency [18]. This method only reflects the short-term supply and provides inadequate information on tissue reserves [16, 18]. Thus, the determination of the transketolase activity and the TDP concentration in erythrocytes are preferred status parameters [17].

Riboflavin supply can be determined by measuring the glutathione reductase activity in erythrocytes, for which FAD is needed as a co-enzyme [16,19,20]. The activity coefficient is calculated from the ratio of enzyme activity with and without FAD addition. Activity coefficients of >1.4 indicate a riboflavin deficiency, while coefficients between 1.2 and 1.4 indicate a marginal deficiency [16]. In the case of a glucose-6-phosphate dehydrogenase deficiency, FAD increasingly binds to the glutathione reductase. As a consequence activity measurement of the enzyme can yield misleading results [19,21].

A further option for the determination of riboflavin supply is the measurement of urinary excretion of riboflavin. Riboflavin excretion in urine reflects the short-term supply [16,19,22] and correlates with riboflavin intake in people with a body nitrogen equilibrium [23]. 24-hour urinary excretion levels of riboflavin between 40 μg and 119 μg are defined as a marginal deficiency, with levels <40 μg being defined as a deficiency [16].

An activity coefficient of <1.2 and a 24-hour urinary excretion of riboflavin at a level ≥120 μg are considered as indicators for an adequate riboflavin supply [16].

Evaluation of *niacin supply* based on dietary intake of niacin equivalents is unreliable due to the differing bioavailability of niacin and its conversion from tryptophan, respectively. The intake of niacin equivalents correlates with the excretion of niacin metabolites in urine. Low excretion of the niacin metabolites N-methyl nicotinamide and N-methyl-2-pyridon-5-carboxamide indicates a low body store. Excretion of niacin metabolites in urine can therefore be seen as a marker of niacin supply [24–27]. Excretion of N-methyl nicotinamide and N-methyl-2-pyridon-5-carboxamide totalling less than 1.5 mg in 24 hours indicates a severe niacin deficiency [28]. As the concentration of N-methyl-2-pyridon-5-carboxamide declines to a higher degree than that of N-methyl nicotinamide as a result of reduced niacin intake, a ratio of less than 1.0 is a further indicator for niacin deficiency [10].

The concentration of niacin metabolites in plasma is less sensitive to changes in intake than the concentration in urine. Based on current knowledge, it is not possible to assess whether the concentration of niacin metabolites in plasma is suitable as a biomarker for niacin supply [29]. Inadequate supply can also be detected based on a decline in NAD concentration in erythrocytes [10]. There are contradictory findings with regard to the relevance of the ratio of NAD to NADP concentrations in whole blood for assessment of niacin supply [10,30].

3. Derivation of the reference values for thiamin, riboflavin, and niacin

3.1. Adults

For the derivation of the reference values for *thiamin* intake, studies primarily investigating the transketolase activity in erythrocytes, and also the excretion of thiamin in urine are used as a basis. A TDP effect of <15% and 24-hour urinary excretion levels of thiamin of >66 μg were taken as a basis for a target value for an adequate thiamin supply [17,19]. Using thiamin balance studies [31–33], the desired level of thiamin excretion in urine and adequate transketolase activity in erythrocytes was achieved given an intake of 0.45 mg thiamin/1000 kcal. This intake is specified as the average requirement [5].

For the derivation of the reference values for *riboflavin* intake, studies primarily investigating the glutathione reductase activity in erythrocytes and also the excretion of riboflavin in urine are used as a basis. An activity coefficient of <1.2 and a 24-hour urinary excretion level of riboflavin of ≥120 μg were taken as a basis for target levels [16]. Investigations

[1] NAD and NADP are abbreviations for the pyridine nucleotides and describe the overall pool, NAD^+ or $NADP^+$ the oxidised form, NADH or NADPH the reduced form.

determined adequate glutathione reductase activity and urinary excretion of riboflavin given a riboflavin intake of approximately 0.5 mg/1000 kcal [34–36]. A riboflavin intake of 0.5 mg/1000 kcal is specified as the average requirement [5].

The reference values for *niacin* intake are derived based on the assumption of an average requirement needed to avoid symptoms of pellagra and to maintain the body's vitamin store. With a niacin equivalent intake of below 4.4 mg/1000 kcal, the body's reserves diminish, measured by diminished urinary excretion of the niacin metabolites N′-methyl nicotinamide and N′-methyl-2-pyridone-5-carboxamide [24,37,38]. In the longer term, symptoms of the deficiency disease pellagra occur. These were not observed with intake levels from around 4 mg/1000 kcal up to 5.4 mg/1000 kcal [11,37–40]. In agreement with professional bodies [29,41–43], an intake of niacin equivalents amounting to 5.5 mg/1000 kcal is suggested as the average requirement to avoid symptoms of pellagra and to maintain the body's reserves [5].

Table 1 shows the resultant recommend intake values for thiamin, riboflavin, and niacin intake, assuming a coefficient of variation of 10%, due to the variation in requirement within the population, and taking into account the guiding values for energy intake [5].

3.2. Infants aged 4 to under 12 months, children, and adolescents

No data are available regarding thiamin, riboflavin, and niacin requirements for infants, children, and adolescents. The reference values for infants aged 4 to under 12 months, children and adolescents are therefore based on the average requirement for adults (see "Adults") and are calculated considering the age-based guiding values for energy intake [5]. Based on the mean requirement for adults and assuming a coefficient of variation of 10%, a recommended intake for thiamin, riboflavin, and niacin is then derived by taking into account the guiding values for energy intake (see Table 1).

3.3. Infants aged 0 to under 4 months

Derivation of the reference values for thiamin, riboflavin, and niacin intake for infants aged 0 to under 4 months is based on the content of the three vitamins in breast milk, which is considered to be the optimal diet for infants [44,45]. The reference values for infants are therefore estimated values. The average breast milk intake of an exclusively breastfed infant is 750 ml/day [46]. Based on a mean vitamin content of breast milk, the estimated values for the intake of thiamin, riboflavin, and niacin for breastfed infants aged *0 to under 4 months* are shown in Table 2.

With regard to the tryptophan content in breast milk, it could be assumed that breast milk supplies further niacin equivalents, as niacin can be formed in the liver from tryptophan (see "Introduction"). Due to the high protein turnover and nitrogen retention during infancy, however, the consideration of niacin equivalents would probably overestimate the contribution of tryptophan [15]. Tryptophan intake is therefore not taken into consideration in the derivation for the reference values for niacin intake for infants.

3.4. Pregnancy

There are no data to suggest that the relationship between thiamin, riboflavin, niacin, and energy requirement for pregnant women is any different from that for women who are not pregnant. Due to the higher guiding value for energy intake during pregnancy (+250 kcal/day in the 2nd trimester and +500 kcal/day in the 3rd trimester [5]) and based on the average requirement for adults, a

Table 1
Guiding values for energy intake [5] and recommended intake values for thiamin (vitamin B_1), riboflavin (vitamin B_2), and niacin.

Age	Guiding values for energy intake (PAL 1.4)		Recommended intake thiamin		Recommended intake riboflavin		Recommended intake niacin	
	kcal/day		mg/day		mg/day		mg equivalents[a]/day	
	m	f	m	f	m	f	m	f
Infants								
0 to under 4 months	550	500	0.2[b]		0.3[b]		2[b,c]	
4 to under 12 months[d]	700	600	0.4		0.4		5	
Children and adolescents[d]								
1 to under 4 years	1200	1100	0.6		0.7		8	
4 to under 7 years	1400	1300	0.7		0.8		9	
7 to under 10 years	1700	1500	0.9	0.8	1.0	0.9	11	10
10 to under 13 years	1900	1700	1.0	0.9	1.1	1.0	13	11
13 to under 15 years	2300	1900	1.2	1.0	1.4	1.1	15	13
15 to under 19 years	2600	2000	1.4	1.1	1.6	1.2	17	13
Adults[d]								
19 to under 25 years	2400	1900	1.3	1.0	1.4	1.1	16	13
25 to under 51 years	2300	1800	1.2	1.0	1.4	1.1	15	12
51 to under 65 years	2200	1700	1.2	1.0	1.3	1.0	15	11
65 years and older	2100	1700	1.1	1.0	1.3	1.0	14	11
Pregnancy[e]								
2nd trimester		2150		1.2		1.3		14
3rd trimester		2400		1.3		1.4		16
Lactation[f]		2400		1.3		1.4		16

[a] 1 mg niacin equivalents = 1 mg niacin = 60 mg tryptophan
[b] Estimated values
[c] This is an estimated value which refers to preformed niacin.
[d] Taking into account the guiding values for energy intake [5] (PAL value 1.4) and the average requirement for thiamin (0.45 mg/1000 kcal), riboflavin (0.5 mg/1000 kcal), and niacin (5.5 mg/1000 kcal) (see "Derivation of the reference values").
[e] Taking into account the guiding value for energy intake for women aged 19 to under 25 years (PAL value 1.4) and additional energy intake of 250 kcal/day during the 2nd trimester and 500 kcal/day during the 3rd trimester of pregnancy [5].
[f] Taking into account the guiding value for energy intake for women aged 19 to under 25 years (PAL value 1.4) and additional energy intake of 500 kcal/day for exclusive breastfeeding during the first 4–6 months [5].

Table 2
Calculation of the estimated values for breastfed infants aged 0 to under 4 months.

0 to under 4 months of age	Vitamin content of breast milk [µg/100 ml]	Breast milk intake [ml/day]	Vitamin intake given a breast milk intake of 750 ml/day [mg/day]	*Estimated value* (rounded) [mg/day]
Thiamin	22[a]	750[b]	0.165	0.2
Riboflavin	0.037[c]	750[b]	0.28	0.3
Niacin	0.2[d]	750[b]	1.5	2

[a] [47–52].
[b] [46].
[c] [47,49,50,53].
[d] [47,50,54].

higher recommended intake is derived assuming a coefficient of variation of 10% (see Table 1).

3.5. Lactation

There are no indications that the relationship between thiamin, riboflavin, niacin, and energy requirement during lactation are any different from those of non-lactating women. Due to the increased energy requirement during lactation (guiding value +500 kcal/day [5]) and based on the average requirement for adults, a correspondingly higher recommended intake is derived assuming a coefficient of variation of 10% (see Table 1).

4. Preventive aspects

In the following, the currently available data on thiamin, riboflavin, and niacin in association with some health-related aspects are briefly described by citing recent systematic reviews, but without performing an evidence judgment based on a systematic literature research. Dietary reference values are aimed at healthy individuals, thus requirements of patients are not being addressed.

A systematic review of the literature published between 1990 and December 2011 investigated the evidence for an association between *thiamin* intake and biomarkers for thiamin supply as well as various diseases [55]. The review identified studies investigating the association between thiamin intake and the risk of Alzheimer's disease, cardiovascular diseases, cataracts, and colon cancer; however, these studies did not meet the inclusion criteria of the review and many of them showed a high risk of bias. Overall, the available data are insufficient to evaluate the association between thiamin intake and the risk of various diseases.

Recent studies show controversial results on the association between *riboflavin* intake and the risk of premenstrual syndrome and cataracts. The data on the relationship between the intake or serum concentration of riboflavin and cancer risk are also inconsistent. For ovarian, stomach, and colorectal cancer as well as endometrial cancer, for example, some but not all studies found an inverse association between the intake or serum concentration of riboflavin and the risk of cancer. No association was observed for the risk of lung, prostate, pancreatic, and breast cancer or renal cell carcinoma. There was no association between riboflavin intake and bone mineral density, fracture risk, and symptoms of overactive bladder, either. Higher riboflavin intake might reduce homocysteine concentration, but this effect can differ between different groups of people as well as depending on genotype [MTHFR(677C → T) polymorphism] [56].

A systematic review of the literature published between 1990 and February 2012 analyzed 13 studies on the relationship between *niacin* intake and numerous end points such as mortality, cancer, cataracts, infertility, and cognitive decline. Significant, inverse associations were only found for Alzheimer's disease, cognitive decline, and nuclear cataracts as well as microalbuminuria and genome damage. However, similar associations were also described for other nutrients, and it should be noted that the intake of niacin strongly correlates with the intake of other B vitamins, that vitamins interact, and that metabolism can depend on genetic polymorphisms, which means it is not possible to draw conclusions for individual vitamins from the available observational studies [57].

5. Discussion and conclusion

The reference values for thiamin, riboflavin, and niacin are derived in consideration of the reference values for energy intake (PAL 1.4) because all three vitamins have important functions as part of energy metabolism. The D-A-CH reference values for these three vitamins slightly differ from the previous ones since the D-A-CH reference values for energy intake have been revised at the same time [1,5].

Other professional bodies also express their reference values for these vitamins in absolute intakes [15,43] and do hardly differ from the updated D-A-CH reference values for thiamin, riboflavin, and niacin. EFSA already published dietary reference values for niacin — the reference values for thiamin and riboflavin are currently under revision. The EFSA population reference intake for niacin equivalents is expressed per energy unit [29].

Data from Germany show that the median intake of thiamin, riboflavin, and niacin are within the range of reference values or significantly higher [58,59]. An adequate supply can be ensured by consuming foods that are naturally rich in thiamin and riboflavin as well as niacin and tryptophan as part of a balanced wholesome diet. For a thiamin-rich diet, whole-grain products such as whole-grain bread with sunflower seeds as well as oat flakes should be consumed on a daily basis. Lean meat is also a good source for thiamin. Various legumes such as mung beans and peas are also suitable as part of a thiamin-rich diet. Although peanuts have a high thiamin content, they should not be used as a primary source for thiamin due to their high energy density. To ensure a *riboflavin-rich diet* milk and dairy products as well as whole-grain products should be consumed on a daily basis. Meat in moderation (max. 300–600 g a week, including sausage) and fish once or twice a week contribute to an adequate supply. Suitable foods to ensure a *diet rich in niacin equivalents* include anchovies, mung beans, peanuts, and offal. Fish (e.g. tuna, salmon, mackerel) and meat also have a high content of niacin equivalents. Mushrooms have a high content of niacin equivalents with a concurrent low tryptophan content [60].

Supplemental intake beyond the recommended amounts has no health benefit and is therefore not recommended.

Conflict of interest

None.

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