Revised D-A-CH reference values for the intake of vitamin B6

Alexandra Jungert, Jakob Linseisen, Karl-Heinz Wagner, Margrit Richter

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Alexandra Jungert[a]   Jakob Linseisen[b, c]   Karl-Heinz Wagner[d]   Margrit Richter[e]
On Behalf of the German Nutrition Society (DGE)

[a]Interdisciplinary Research Center for Biosystems, Land Use and Nutrition (IFZ), Biometry and Population Genetics, Justus Liebig University, Giessen, Germany; [b]Chair of Epidemiology, Ludwig-Maximilians University of Munich, Augsburg, Germany; [c]Clinical Epidemiology, Helmholtz Zentrum München (HMGU), Neuherberg, Germany; [d]Department of Nutritional Sciences, University of Vienna, Vienna, Austria; [e]Department of Science, German Nutrition Society (DGE), Bonn, Germany

Abstract
Background: The Nutrition Societies of Germany, Austria, and Switzerland as the joint editors of the "D-A-CH reference values for nutrient intake" have revised the reference values for vitamin B$_6$ in summer 2019. *Summary:* For women, the average requirement (AR) for vitamin B$_6$ intake was derived on the basis of balance studies using a pyridoxal-5′-phosphate (PLP) plasma concentration of ≥30 nmol/L as a biomarker of an adequate vitamin B$_6$ status. The recommended intake (RI) was derived considering a coefficient of variation of 10%. The RIs of vitamin B$_6$ for men, children, and adolescents were extrapolated from the vitamin B$_6$ requirement for women considering differences in body weight, an allometric exponent, growth factors as appropriate, and a coefficient of variation. For infants aged 0 to under 4 months, an estimated value was set based on the vitamin B$_6$ intake via breast feeding. The reference value for infants aged 4 to under 12 months was extrapolated from the estimated value for infants under 4 months of age and the average vitamin B$_6$ requirement for adults. The reference values for pregnant and lactating women consider the requirements for the foetus and the loss via breast milk. ***Key Messages:*** According to the combined analysis of 5 balance studies, the AR for vitamin B$_6$ to ensure a plasma PLP concentration of ≥30 nmol/L is 1.2 mg/day for adult females and the extrapolated AR for adult males is 1.3 mg/day. The corresponding RIs of vitamin B$_6$ are 1.4 mg/day for adult females and 1.6 mg/day for adult males, independent of age. For infants, the estimated value is 0.1 mg/day and 0.3 mg/day, depending on age. The AR of vitamin B$_6$ for children and adolescents ranges between 0.5 and 1.5 mg/day, and the RI is between 0.6 mg/day and 1.6 mg/day. During pregnancy, the AR is 1.3 mg/day in the first trimester and 1.5 mg/day in the second and third trimesters; the RI is 1.5 mg/day in the first trimester and 1.8 mg/day in the second and third trimesters. For lactating women, the AR is 1.3 mg/day and the RI is 1.6 mg/day.

Introduction

Reference Values for Nutrient Intake

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 aris-

Margrit Richter,
Department of Science, German Nutrition Society
Godesberger Allee 18
DE–53175 Bonn (Germany)
corresponding_author@dge.de

es from the initial letters of the common country identification for the countries Germany [D], Austria [A], and Switzerland [CH]). Reference value is a collective term for recommended intake (RI), estimated values, and guiding values. The starting point for the derivation of reference values is the determination of the average requirement (AR). The experimentally ascertained AR assumes to meet the needs of the daily nutrient intake of 50% of a defined group of people. For the derivation of the RI, 20–30% is added to the AR what corresponds to 2 standard deviations or a variation coefficient of 10–15%. Thus, a RI value, according to its definition, meets the requirement of nearly any person (approximately 98%) of sex- and age-stratified population groups. Estimated values are given when human requirements cannot be determined with desirable accuracy. Guiding values are given as orientation [1, 2].

Reference values for nutrient intake are amounts that are assumed to

- protect nearly all healthy individuals in a population from deficiency-related conditions,
- ensure optimal physiological and psychological performance, and
- create a certain body reserve [1].

The reference values should be revised regularly. Since 2012, the D-A-CH nutrition societies have published revised reference values for the intake of several nutrients [3–13] but not yet for vitamin B_6. The last update of the reference values for vitamin B_6 given by the D-A-CH nutrition societies dates to a report in 2000 [14]. In summer 2019, the revised reference values for vitamin B_6 intake were published in German. This paper provides a summary of this work.

Vitamin B_6

Vitamin B_6 is one of the water-soluble vitamins [15]. The term refers to a group of 2-methyl-3-hydroxy-5-hydroxymethyl pyridine compounds with pyridoxine activity, including pyridoxine (PN), pyridoxamine (PM), and pyridoxal (PL) as well as their phosphoric acid esters pyridoxine 5′-phosphate (PNP), pyridoxamine 5′-phosphate (PMP), and pyridoxal 5′-phosphate (PLP) [16].

Physiologically, PLP and PMP function as cofactors for enzymes of the amino acid metabolism [16]. In addition, vitamin B_6 plays a role in metabolism of carbohydrates [17], conversion of niacin to tryptophan [18], and synthesis of sphingolipids [19], 5-aminolevulinic acid (a precursor of haemoglobin) [20], and neurotransmitters [21]. Together with riboflavin, folate, and cobalamin, vitamin B_6 regulates homocysteine metabolism [22]. In this context, PLP is required for the conversion of 5,10-methylenetetrahydrofolate from tetrahydrofolate and thus for the remethylation of homocysteine to methionine [22]. Within the transsulfuration pathway, vitamin B_6 is involved in the degradation of homocysteine to cysteine [22].

The vitamin B_6 content in foods was found to be affected by freezing, cooking, and further processing, albeit the extent of the losses varied depending on the assessed compound [23]. The absorption rate of vitamin B_6 depends on the diet. Vitamin B_6 from animal-based foods has a higher bioavailability than vitamin B_6 from plant-based foods [24] due to the lower bioavailability of pyridoxine-5′-β-d-glucoside (PNG) found in plant-based foods compared to PN [24–26]. The estimated bioavailability of free PN is ≥95% [27, 28], while the average bioavailability of PNG is 50–58% [25, 26]. Depending on the kind of food, the PNG proportion of the total vitamin B_6 content ranges between 0 and 82% [24]. With a mixed diet containing 2.3 mg of vitamin B_6 per day, the average absorption rate of vitamin B_6 is 75%, based on measurements of plasma PLP concentration and 24-h urinary vitamin B_6 excretion in men [27].

The average vitamin B_6 pool in the human body is estimated to be ~1,000 μmol (167 mg), whereupon up to 80% of the vitamin B_6 is located in the muscle [29, 30]. The majority of vitamin B_6 in the muscle is found as PLP bound to glycogen phosphorylase [21, 29]. The vitamin B_6 pool in muscle is relatively stable, even at a low-vitamin B_6 diet for 6 weeks [31]. In plasma, vitamin B_6 exists primarily as PLP [32] bound to albumin [33]. In erythrocytes, PLP binds to haemoglobin [16]. Free PLP can be dephosphorylated by alkaline phosphatase to PL, which is capable of crossing biological membranes [16].

There is a sigmoidal relationship between vitamin B_6 intake and plasma PLP concentration [27]. Plasma PLP concentration reaches a new equilibrium ~10 days after PN supplementation [34] or about 14 days after changing dietary vitamin B_6 intake [27]. The half-life of vitamin B_6 is 2–6 weeks; around 2–3% of the vitamin B_6 pool are lost per day [35]. 4-Pyridoic acid (4-PA) is the major catabolic metabolite with a proportion of up to 85% of the total vitamin B_6 excretion via urine [34].

Criteria to Assess the Supply with Vitamin B_6

Vitamin B_6 status can be determined directly by biomarkers, for example, concentrations of PL, PMP, or PLP in plasma or erythrocytes, and total vitamin B_6 or 4-PA

concentrations in urine [16]. Currently, plasma PLP concentration is considered to be the best status parameter [28]. It correlates with both vitamin B_6 intake [36–38] and vitamin B_6 concentration in tissue [34]. A deficient vitamin B_6 status is assumed for PLP concentrations <20 nmol/L. PLP concentrations between 20 and 30 nmol/L indicate a marginal status and PLP concentrations >30 nmol/L an adequate supply [39]. In intervention studies in healthy subjects who received a low-vitamin B_6 diet (<0.5 mg vitamin B_6 per day), changes in the amino acid profile and in the metabolism of one-carbon units and tryptophan occurred at PLP concentrations <30 nmol/L [39, 40]. It has to be considered that inflammation [41–43], a low albumin concentration, and a high alkaline phosphatase activity may have a negative impact on PLP concentration [16]. Lifestyle factors like smoking and alcohol intake are considered to be influencing factors as well [43–45]. Current and former smokers show frequently lower PLP concentrations than subjects who had never smoked what might be a result of oxidative stress caused by smoking [43]. Some studies reported a positive association between vitamin B_6 status parameters and alcohol consumption [46, 47]. This observation might be explained by a higher vitamin B_6 intake due to the consumption of alcoholic beverages or changes in transsulfuration and methylation processes [46]. In contrast, chronic alcohol abuse is associated with lower PLP concentrations [44], probably due to an impairment of liver function [45].

Since vitamin B_6 is important for amino acid metabolism, it was proposed that the requirement for vitamin B_6 is linked to protein intake [48]. However, due to inconsistent results, different study designs, and varying protein intake levels [48–52], no influence of protein intake on vitamin B_6 requirements of subjects following a usual mixed diet is assumed.

Derivation of the Reference Values for the Intake of Vitamin B_6

Adults

Adults under 65 Years of Age

The reference values for vitamin B_6 intake in adults under 65 years of age were derived based on the intake levels that are required for a plasma PLP concentration of ≥30 nmol/L. According to the results of intervention studies, daily intakes of 1.3–1.5 mg vitamin B_6 are sufficient to achieve a PLP concentration of ≥30 nmol/L in the majority of women, even at a daily protein intake of 1.2

Table 1. Recommended intake values for vitamin B_6

Age	Vitamin B_6, mg/day	
	male	female
Infants[a]		
0 to under 4 months	0.1	
4 to under 12 months	0.3	
Children and adolescents		
1 to under 4 years	0.6	
4 to under 7 years	0.7	
7 to under 10 years	1.0	
10 to under 13 years	1.2	
13 to under 15 years	1.5	1.4
15 to under 19 years	1.6	1.4
Adults		
19 to under 25 years	1.6	1.4
25 to under 51 years	1.6	1.4
51 to under 65 years	1.6	1.4
65 years and older	1.6	1.4
Pregnant women		
1st trimester		1.5
2nd and 3rd trimesters		1.8
Lactating women		1.6

[a] Estimated values.

or 1.55 g/kg body weight reported in some of these intervention trials [37, 53–55]. According to the combined analysis of 5 balance studies [37, 49, 53–55], the average vitamin B_6 requirement to ensure a plasma PLP concentration of ≥30 nmol/L is 1.2 mg/day, considering the higher bioavailability of synthetic PN [37]. Assuming a coefficient of variation of 10% (addition of 20%), the RI for women aged 19 to under 65 years is 1.4 mg/day (Table 1).

As there are no convincing balance studies in men, their requirement was extrapolated from the derived requirement in women. Assuming that vitamin B_6 requirement depends on the metabolically active body mass [28], and taking into account an allometric exponent, the AR in men is 1.4 mg/day. Allometric scaling is based on the association between body mass and metabolism. According to Kleiber's law, the metabolism scaled with a potency of 0.75 of body mass [56, 57]. Due to the dependence of B vitamins on the metabolic body mass, an allometric exponent of 0.75 is included in the calculation. Considering a coefficient of variation of 10% (addition of 20%), the RI for men aged 19 to under 65 years is 1.6 mg/day (Table 2).

Table 2. Derivation of the average requirement and recommended intake values for vitamin B_6 for men ≥19 years of age considering differences in average body weight and an allometric exponent

Age	Reference body weight male,[a] kg [1]	Reference body weight female,[a] kg [1]	Average vitamin B_6 requirement considering reference body weight and allometric exponent, mg/day[b]	Coefficient of variation 10% (addition of 20%), mg/day	Recommended intake for vitamin B_6 (rounded), mg/day
19 to under 25 years	70.8	60.5	1.35	1.62	1.6
25 to under 51 years	70.7	60.0	1.36	1.63	
51 to under 65 years	68.7	58.2	1.36	1.63	
65 years and older	66.8	57.1	1.35	1.62	

[a] Reference values for body weight are calculated from the median body height determined in the *German Health Interview and Examination Survey for Adults* (DEGS1) corresponding to a BMI of 22 kg/m^2 [1]. Based on data of DEGS1, the median body heights were 179.4, 179.2, 176.7, and 174.2 cm for male subjects in the age groups 18–29, 30–39, 50–59, and 60–69 years, respectively [97]. For female subjects, the median body heights were 165.8, 165.1, 162.6, and 161.1 cm in the respective age groups [97]. These median values were used for the appropriate age groups mentioned in this table, albeit the age classification is not entirely homogeneous. [b] Calculated from: average requirement$_{women}$ [mg/day] × (reference body weight$_{men}$ [kg]/reference body weight$_{women}$ [kg])$^{allometric\ exponent}$ [28]; average requirement$_{women}$: 1.2 mg/day; allometric exponent: 0.75.

Adults above 65 Years of Age

Several cross-sectional studies showed an inverse association between age and PLP concentration [38, 51, 58–61]; others, however, did not [32, 62, 63]. In a long-term study including 360 subjects ≥60 years of age, no decrease of the PLP concentration with advancing age was observed [52]. Possible causes discussed for lower PLP concentrations in elderly people comprise lower vitamin B_6 intake, reduced albumin synthesis, inflammation, and increased alkaline phosphatase activity [16, 36, 62]. However, age-related changes of vitamin B_6 bioavailability or metabolism have not been proven so far [36, 62]. In a study including 12 subjects aged >60 years, the vitamin B_6 intake level was estimated that was required at different protein intakes to regain the baseline plasma PLP concentration after a low-vitamin B_6 diet [50]. In 2 women and 1 man who had a daily protein intake of 0.8 g/kg body weight, this required a vitamin B_6 intake of 1.33 mg/day (women) and 1.36 mg/day (men), respectively. Due to the small sample size and the fact that baseline PLP concentrations exceeded 30 nmol/L [50], the RI for adults above 65 years of age is 1.4 mg/day for women and 1.6 mg/day for men (Table 1) and thus corresponds to the reference values of younger adults.

Children and Adolescents

No data from balance studies are available regarding the vitamin B_6 requirement for children and adolescents. Therefore, the reference values for children and adolescents are based on the values compiled for adults and take into account differences in body weight, an allometric ex-

ponent, growth factors to consider the requirements for growth, and a coefficient of variation of 10% (addition of 20%) (Table 3). Growth factors at the different age groups were calculated from the protein requirement for growth in relation to the maintenance requirement according to the World Health Organization (WHO) [14, 64]. When using the age groups and reference body weights the D-A-CH reference values are based upon [1], the AR values range between 0.5 and 1.5 mg/day. The resulting RI values for vitamin B_6 range from 0.6 mg/day (for 1 to under 4-year-olds) to 1.4 mg/day for female adolescents and 1.6 mg/day for male adolescents (15 to under 19-year-olds) (Tables 1, 3). We want to point out that the calculated values for adolescents aged 15 to under 19 years are higher than those for adults (Table 3). However, as no evidence of a higher vitamin B_6 requirement for adolescents exists, the RI values for female and male adolescents aged 15 to under 19 years are assumed to be the same as for adults (Table 3).

Infants

The reference values for the intake of vitamin B_6 for infants aged 0 to under 4 months were derived based on the vitamin B_6 content of breast milk, which is considered to be the optimal diet for infants [65, 66]. The reference values for infants are therefore estimated values.

The average vitamin B_6 content from 2 studies of mature milk from lactating women not supplementing vitamin B_6 is 0.145 mg/L [67, 68]. Assuming an average breast milk intake of 750 mL/day [69], vitamin B_6 intake in an exclusively breastfed infant is approximately 0.109 mg vi-

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Table 3. Derivation of the average requirement and recommended intake values for vitamin B_6 for children and adolescents considering differences in average body weight, an allometric exponent, and growth factors

Age	Sex	Reference body weight,[a] kg [1]	Growth factor[b] [1]	Average vitamin B_6 requirement considering reference body weight, allometric exponent, and growth factor,[c] mg/day	Coefficient of variation 10% (addition of 20%), mg/day	Recommended intake for vitamin B_6 (rounded), mg/day
1 to under 4 years	Male	13.9	0.25	0.52	0.62	
	Female	13.2	0.25	0.48	0.58	0.6
4 to under 7 years	Male	20.2	0.06	0.58	0.70	
	Female	20.1	0.06	0.56	0.67	0.7
7 to under 10 years	Male	29.3	0.13	0.82	0.98	
	Female	28.7	0.13	0.78	0.94	1.0
10 to under 13 years	Male	41.0	0.13	1.05	1.26	
	Female	42.1	0.11	1.02	1.23	1.2
13 to under 15 years	Male	55.5	0.10	1.28	1.54	1.5
	Female	54.0	0.07	1.19	1.42	1.4
15 to under 19 years	Male	69.2	0.07	1.47	1.77	1.6[d]
	Female	59.5	0.02	1.22	1.46	1.4[d]

[a] Reference values for body weight correspond to the median body weight determined in the *German Health Interview and Examination Survey for Children and Adolescents in Germany* (KiGGS; 2003–2006) [98]. In each case, the values reflect the midpoint of the respective age range. [b] Growth factors at the different ages were calculated as the proportional increase in protein requirement for growth relative to the maintenance requirement according to the WHO [14, 64]. [c] Calculated from: average requirement$_{adults}$ [mg/day] × (reference body weight$_{children/adolescents}$ [kg]/reference body weight$_{adults}$ [kg])$^{allometric\ exponent}$ × (1 + growth factor$_{children/adolescents}$) [28]; average requirement$_{adults}$: male 1.4 mg/day, female 1.2 mg/day; reference body weight$_{adults}$ (age group 25 to under 51 years): men 70.7 kg, women 60.0 kg [1]; allometric exponent: 0.75. [d] For adolescents aged 15 to under 19 years, the reference value is assumed to be the same as for adults (see Table 1), as there is no evidence of a higher requirement.

tamin B_6/day. This intake is sufficient to ensure a PLP concentration of ≥30 nmol/L [68]. Therefore, the estimated value for adequate vitamin B_6 intake is 0.1 mg/day for infants aged 0 to under 4 months.

For infants aged 4 to under 12 months, data on the average vitamin B_6 requirement are lacking. Thus, in line with the approach of the European Food Safety Authority (EFSA) [28], the vitamin B_6 reference value for infants of this age group is derived by averaging the results of the extrapolation from the estimated value for infants under 4 months of age and of the extrapolation from the AR for adults. Based on the estimated value for infants under 4 months of age (0.1 mg/day), considering differences in body weight [1] and the allometric exponent, the vitamin B_6 intake is 0.14 mg/day. However, based on the average vitamin B_6 requirement for adults (1.2 mg/day for women and 1.4 mg/day for men), considering differences in body weight, the allometric exponent, and the growth factor [1], the vitamin B_6 intake is 0.45 mg/day for female infants and 0.49 mg/day for male infants. By calculating the

arithmetic mean, an estimated value for an adequate vitamin B_6 intake of 0.3 mg/day is derived (Table 4).

Pregnancy

Plasma PLP concentration decreases during pregnancy; especially in the third trimester, concentrations <20 nmol/L were observed [70–72]. Possible reasons are haemodilution, enhanced PLP transfer to the foetus, increased alkaline phosphatase activity, and a higher requirement due to tissue growth [72, 73]. In line with the EFSA [28], the requirement during pregnancy is derived on the basis of body weight gain and average tissue content of vitamin B_6. Based on weight gain during pregnancy (16.7 g/day in the first, 60.6 g/day in the second, and 54.2 g/day in the third trimester [1]), a vitamin B_6 requirement of 15 nmol/g tissue growth (3.7 mg/kg) [30] and an average bioavailability of 75%, the AR is 1.3 mg/day in the first trimester and 1.5 mg/day in the second and third trimesters. After taking a coefficient of variation of 10% (addition of 20%) into account, the recommended vitamin

Table 4. Derivation of the estimated value for the intake of vitamin B_6 for infants aged 4 to under 12 months

Age	Sex	Reference body weight,[a] kg [1]	Derivation based on the estimated value for infants under 4 months of age: vitamin B_6 intake considering reference body weight and allometric exponent,[b] mg/day	Derivation based on the average vitamin B_6 requirement for adults: vitamin B_6 intake considering reference body weight, allometric exponent, and growth factor,[c] mg/day	Averaged vitamin B_6 intake considering both extrapolation paths, mg/day	Estimated value for the vitamin B_6 intake (rounded), mg/day
4 to under 12 months	Male	8.6	0.14	0.49	0.31	0.3
	Female	7.9	0.14	0.45	0.29	

[a] Reference values for body weight correspond to the median body weight of the WHO child growth standards [99] for the age of 8 months. [b] Calculated from: estimated value$_{0-4 \text{ months}}$ [mg/day] × (reference body weight$_{4-12 \text{ months}}$ [kg]/reference body weight$_{0-4 \text{ months}}$ [kg])$^{\text{allometric exponent}}$ according to [28]; estimated value$_{0-4 \text{ months}}$: 0.1 mg/day (see Table 1); reference body weight$_{0-4 \text{ months}}$: male 5.6 kg, female 5.1 kg [1]; allometric exponent: 0.75. [c] Calculated from: average vitamin B_6 requirement$_{\text{adults}}$ [mg/day] × (reference body weight$_{4-12 \text{ months}}$ [kg]/reference body weight$_{\text{adults}}$ [kg])$^{\text{allometric exponent}}$ × (1 + growth factor$_{0-4 \text{ months}}$) according to [28]; average vitamin B_6 requirement$_{\text{adults}}$: male 1.4 mg/day, female 1.2 mg/day; reference body weight$_{\text{adults}}$ (age group 25 to under 51 years): male 70.7 kg, female 60.0 kg [1]; allometric exponent: 0.75; growth factor$_{4-12 \text{ months}}$: 0.7 [1].

B_6 intake for pregnant women is 1.5 mg/day in the first trimester and 1.8 mg/day in the second and third trimesters.

Lactation

Vitamin B_6 concentration of breast milk is influenced by the mother's diet [67]. Based on a vitamin B_6 secretion with breast milk of 0.1 mg/day (see the section Infants), an average bioavailability of 75% and an average breast milk intake of 750 mL/day of an exclusively breastfed infant, the AR in lactating women is 1.3 mg/day. Considering a coefficient of variation of 10% (addition of 20%), the recommended vitamin B_6 intake is 1.6 mg/day.

Preventive Aspects

In the following, the available data on health-related aspects of vitamin B_6 are outlined without an evidence judgement. As most studies do not investigate vitamin B_6 alone but in combination with other B vitamins, it is sometimes not possible to evaluate the unique role of the different B vitamins.

Several epidemiological long-term studies repeatedly demonstrated inverse associations between vitamin B_6 status or vitamin B_6 intake and risk of depression [74], cardiovascular diseases [75], and cognitive impairment [76, 77]. Furthermore, an inverse association between vitamin B_6 status and inflammation has been described [41, 43, 78]. Meta-analyses of epidemiological studies indicate negative associations for both dietary vitamin B_6 intake

and PLP concentration with the general risk of cancer and specifically the risk of cancers of the gastrointestinal tract such as the colorectum [79, 80], oesophagus, stomach, and pancreas [80]. Another meta-analysis indicates a negative association between the PLP concentration and the risk of breast cancer in postmenopausal women [81]. However, an association between vitamin B_6 intake and risk of breast cancer could not be proven [81].

So far, most intervention studies could not confirm preventive effects of vitamin B_6 regarding risk of cancer, depression, cardiovascular diseases, impairment of cognitive functions in older age or Alzheimer's disease, or an effect on bone remodelling [80, 82–89]. Based on available data, a vitamin B_6 intake exceeding the reference values is not clearly associated with preventive effects on health in the general population.

Discussion and Conclusion

Within the present revision of the D-A-CH reference values for the intake of vitamin B_6, the method of derivation has been changed: it is now based on balance studies using plasma PLP concentration as a biomarker to determine the AR. Reliable data on the vitamin B_6 intake levels that are sufficient to achieve the desirable plasma PLP concentration of 30 nmol/L are available for women, but not for children, adolescents, and men. Therefore, the reference values for children and adolescents were derived from the data for women considering differences in body weight and increased requirements in children and ado-

lescents due to growth. Likewise, the reference values for men were derived based on the AR of women with consideration of differences in body weight. Due to the changed derivation, the reference values for some age groups are slightly higher than before. For pregnancy and lactation, the reference values are somewhat lower. However, higher intake levels for pregnant women compared to non-pregnant women are now recommended already in the first trimester, whereas previously higher intake levels were recommended from the beginning of the second trimester.

The derivation and magnitude of the revised reference values show similarities as well as differences to the derivation and magnitude of reference values set by the EFSA [28], Institute of Medicine (IOM) [90], and WHO [91]. For infants, the D-A-CH reference values for vitamin B_6 are in line with the reference values set by EFSA, IOM, and WHO, whereas for other age categories as well as for pregnant and lactating women, differences can be noted.

Similarities regarding the derivation include (1) the absence of connecting the vitamin B_6 requirements to the protein intake levels, (2) the use of the circulating PLP concentration as a biomarker for vitamin B_6 status, (3) the extrapolation of the ARs for children, adolescents, and pregnant/lactating women from the ARs of adults, (4) the vitamin B_6 content in human milk as a basis for deriving reference values for infants, (5) the higher AR for pregnancy and lactation due to foetus requirements and milk secretion, respectively, and (6) the nature of the reference values, that is, adequate intake and estimated values for infants and RIs for adolescents and adults.

The differences include, for instance, (1) cut-off values for defining adequate PLP concentrations, (2) age categories, reference body weights, and growth factors, (3) age at which sex-specific reference values were applied, (4) requirements of older adults, and (5) reference values depending on trimester. More precisely, IOM [90] and WHO [91] use a PLP concentration of ≥20 nmol/L to define an adequate vitamin B_6 status and also consider studies analyzing other vitamin B_6 biomarkers, such as activation coefficients of erythrocyte aspartate aminotransferase and erythrocyte alanine aminotransferase as well as homocysteine concentration and the renal excretion of tryptophan metabolites following a tryptophan loading test to derive ARs for adults, respectively. In contrast, EFSA bases the derivation of ARs on the achievement of a PLP concentration of ≥30 nmol/L [28] similar to the here presented derivation. With respect to the age groups, the D-A-CH reference values for children and adolescents are stratified into 7 age groups, whereas IOM [90]

and WHO [91] use only 4 and EFSA [28] applies 5 age groups. This and the fact that different population studies were quoted as source of the reference body weights and growth factors explain why the age at which sex-specific reference values were set differs among the authorities. With reference to the above-mentioned study by Ribaya-Mercado et al. [50], IOM [90] and WHO [91] assume that older subjects require a higher vitamin B_6 intake to maintain a sufficient vitamin B_6 state compared to young adults and thus set age-specific reference values for adults. EFSA [28] abstains from setting age-specific reference values in adulthood but takes the results from Ribaya-Mercado et al. [50] into account by applying an AR of 1.3 mg/day for women and, after extrapolation, 1.5 mg/day for men. In contrast, D-A-CH nutrition societies conclude that the evidence is insufficient to set a higher AR and in consequence RI for older adults. In terms of pregnancy, the here presented D-A-CH reference values for pregnant women are the only ones that imply a trimester-specific vitamin B_6 intake, although EFSA [28], IOM [90], and WHO [91] acknowledge that the lower vitamin B_6 state is particularly evident in late gestation. In contrast to EFSA [28], IOM [90], and WHO [91], the D-A-CH reference values are based on trimester-specific weight gain during pregnancy taking into account that vitamin B_6 requirements rely on tissue growth.

According to representative data from the German National Nutrition Survey II, the median vitamin B_6 intake is 1.2 mg/day in women and 1.6 mg/day in men [92, 93]. This means that the recommended vitamin B_6 intake of 1.4 mg/day for women and 1.6 mg/day for men is not achieved by parts of the general adult population in Germany. Using the PRIs set by EFSA [28], that is, 1.6 mg/day for women and 1.7 mg/day for men, the situation appears even more critical, particularly for female subjects. However, irrespectively of the applied reference value, a vitamin B_6 intake below the RI does not necessarily represent a state of vitamin B_6 deficiency; rather it indicates a higher risk of suboptimal intake. The aim of reference values is the adequate nutrient supply of the healthy individuals in a population. The RI meets the requirements of ∼98% of the population. Thus, the RI exceeds the actual requirements of most people. Therefore, the RI is not suitable to distinguish between an adequate and inadequate nutrient intake on individual level or to diagnose a state of nutrient deficiency. For the examination of the probability that the usual intake of an individual is inadequate or to estimate the prevalence of inadequate intake in groups, the AR can be used [94, 95]. Referring to the AR, the above-mentioned median vitamin B_6 intake levels found in the Ger-

man National Nutrition Survey II are in line with the AR for women and exceeded the AR for men. In light of this and the fact that the nutrient data base used to calculate the vitamin B_6 intake levels in the German National Nutrition Survey II considered predominantly non-fortified foods, vitamin B_6 is apparently no critical nutrient for the general population. However, the diagnosis of a deficiency should base on a comprehensive individual assessment including the measurement of recognized biomarkers, such as plasma PLP concentration for vitamin B_6.

Several protein-rich foods are good vitamin B_6 sources [16]. High levels of vitamin B_6 can be found in fish, such as sardines (cooked: 0.92 mg/100 g) and mackerels (cooked: 0.59 mg/100 g), as well as meat products, such as beef liver (cooked: 0.91 mg/100 g) [96]. In addition, cereals (e.g., whole-wheat flour: 0.46 mg/100 g), nuts (e.g., hazelnut: 0.66 mg/100 g and walnuts: 0.60 mg/100 g), dried fruits (banana: 0.93 mg/100 g and mango: 0.51 mg/100 g), and some vegetables (e.g., raw red pepper: 0.45 mg/100 g) contain relatively high amounts of vitamin B_6 [96]. However, as pointed out previously, plant-based foods show sometimes high amounts of PNG [24]. For instance, high levels of PNG were noticed in frozen cauliflower/broccoli, cooked soy beans, raisins, fresh orange juice, and carrots with around two-thirds of the total vitamin B_6 content [24]. In contrast, the PNG proportion in walnuts, whole-wheat flour, bananas, and raw cauliflower is expected to be below 20% [24]. In a mixed diet, PNG usually accounts for approximately 15% of the total vitamin B_6 amount [26]. Thus, a mixed diet can provide adequate amounts of vitamin B_6 under the assumption of a bioavailability of 75%. The bioavailability was taken into account by the D-A-CH nutrition societies when setting the reference values. To achieve adequate vitamin B_6 supply, the daily intake of whole-grain products, vegetables, and fruits including a portion of nuts is recommended. Intake of fish once to twice a week and a low amount of meat can also contribute to cover the vitamin B_6 requirement.

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