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New Reference Values for Vitamin C Intake

German Nutrition Society (DGE), Bonn, Germany

Key Words
Vitamin C · Ascorbic acid · Dietary intake · Reference value

Abstract
The German, Austrian, and Swiss nutrition societies are the editors of the 'reference values for nutrient intake'. They have revised the reference values for the intake of vitamin C and published them in February 2015. The average vitamin C requirement in healthy adults is considered to be the vitamin C amount that compensates for the metabolic losses of vitamin C, and ensures a fasting ascorbate plasma level of 50 µmol/l. Based on the present data from studies with non-smoking men, metabolic losses of 50 mg/day are assumed, as well as an absorption rate of 80% and an urinary excretion of 25% of the vitamin C intake. Taking this into account, the calculated average requirement in men is 91 mg/day. Considering a coefficient of variation of 10%, a reference value (recommended intake) of 110 mg/day for men is derived. The vitamin C requirement in women as well as in children and adolescents is extrapolated from the requirement in men and in relation to their body weight. This results in a recommended intake of about 95 mg/day for adult women. Because the requirement in pregnant and lactating women is increased, higher recommended intakes are derived for them, 105 mg/day for pregnant women from the fourth month on and 125 mg/day for lactating women, respectively. For boys and girls at the age of 1 to under 15 years, there are increasing recommended intake values from 20 to 85 mg/day. For male and female adolescents, at the age of 15 to under 19 years, the recommended intake is 105 and 90 mg, respectively. As smokers have higher metabolic losses and lower plasma levels of vitamin C than non-smokers (turnover is 40% higher), the reference value for vitamin C intake is set to 135 mg/day for female smokers and 155 mg/day for male smokers. For infants in their first year of life, the reference value (estimated value) is set to 20 mg vitamin C/day, based upon the lowest observed vitamin C intake for infants in the United Kingdom and the United States, that obviously meets the requirement in infants and that is 3 times higher than the amount necessary to prevent scurvy (7 mg/day).

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 arises from the initial letters of the common country identification for the countries Germany (D), Austria (A) and Switzerland (CH)). Currently, the 'reference values for nutrient intake' are being revised. Following the revised reference values for vitamin D [2], calcium [3] and folate [4], the revised reference values for vitamin C (table 1) were published in February 2015.

Vitamin C (ascorbic acid) is a highly effective reducing agent in many intra- and extracellular reactions. Vitamin C is a cofactor of copper- and iron-dependent enzymes. It is also involved in the synthesis of collagen, L-carnitine,

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E-Mail karger@karger.com
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Angela Bechthold
Department of Science
German Nutrition Society
Godesberger Allee 18, DE–53175 Bonn (Germany)
E-Mail bechthold@dge.de

Table 1. Reference values for vitamin C intake (recommended intake) [1]

Age	Vitamin C, mg/day	
	m	f
Infants[a]		
0 to under 4 months	20	
4 to under 12 months	20	
Children and adolescents		
1 to under 4 years	20	
4 to under 7 years	30	
7 to under 10 years	45	
10 to under 13 years	65	
13 to under 15 years	85	
15 to under 19 years	105	90
Adults[b]		
19 to under 25 years	110	95
25 to under 51 years	110	95
51 to under 65 years	110	95
65 years and older	110	95
Pregnant women		
From 4th month on		105
Lactating women		125

[a] Estimated values; [b] smokers: 155 mg/day (men) and 135 mg/day (women), respectively.

and catecholamines, as well as in tyrosine formation and the peptide amidations that are necessary for the activity of hormones like oxytocin [5, 6]. Vitamin C is a strong antioxidant that scavenges free radicals and other reactive oxygen and nitrogen species such as superoxide, hydroxyl radicals and hypochlorous acid. Thus, it protects biomolecules like lipids and possibly also the DNA against oxidative damage [6–8].

Criteria for the Assessment of Vitamin C Supply

Plasma Ascorbate Concentration

Vitamin C is transported as the free anion ascorbate in plasma. The plasma ascorbate concentration is a suitable indicator of the vitamin C status. It is a biomarker for current vitamin C intake, and the fasting plasma ascorbate concentration is a biomarker for the total body pool and long-term intake of vitamin C.

When the vitamin C intake increases, the plasma ascorbate concentration increases according to a sigmoidal (S-shaped) curve [9–13]. The plasma ascorbate concentration is characterised by a steep rise, up to about 50 μmol/l, when vitamin C intake is between 60 and 100 mg/day. At higher intake levels, it reaches a plateau at about 70–80 μmol/l due to decreased absorption rates and increased excretion. Women reach this plateau at lower vitamin C intake levels than men [14–16].

The plasma ascorbate concentration is limited by the maximum rate of renal tubular reabsorption (reabsorption capacity), which is about 1.5 mg/100 ml [17]. During deficiency, the renal tubular reabsorption rate is increased, indicating a certain adaption to the vitamin C body pool [18].

When, at high intake levels, the plasma concentration ranges in the flattening part of the sigmoidal curve (>50 μmol/l), the plasma concentration is of limited value as a biomarker [19]. The biomarker is also affected by smoking, pregnancy, age, gender and presence of infections, with usually lower plasma ascorbate levels in smokers [20–22], men, pregnant women [23, 24], elderly people (e.g. due to reduced intake, chronic disease; there is no effect of aging itself [25]) and people with infections [19, 26, 27]. The plasma ascorbate concentration is also influenced by the genotype (polymorphism). Polymorphisms in the genes encoding sodium-dependent vitamin C transport proteins are strongly associated with plasma ascorbate levels and likely impact tissue cellular vitamin C status. Some limited data exist on the influence of genetic changes in manganese superoxide dismutase (SOD_2) and glucose transport proteins (SLC_2) on ascorbate levels in humans [28].

A plasma ascorbate concentration of 50 μmol/l or higher is considered to represent an adequate status (see 'fulfillment of the functions of vitamin C, saturation of body pools and renal reabsorption capacity'). Plasma ascorbate concentrations between 10 and 50 μmol/l indicate a suboptimal status with an increased risk of deficiency [26]. Plasma ascorbate concentrations below 20 μmol/l are often associated with subclinical symptoms [29]. The subclinical signs of an insufficient vitamin C supply are non-specific; the earliest sign is general fatigue. Additionally, muscle weakness, lethargy and anaemia occur [30].

Immunocompetent Cells

The concentration in blood cells (neutrophils, monocytes, thrombocytes, lymphocytes) is also associated with the intake of vitamin C. In non-smoking women and men, the intracellular ascorbate concentration reaches saturation at intake levels from about 100 mg vitamin C/day (neutrophils about 1.3 mmol/l, monocytes about 3 mmol/l, thrombocytes about 3.5 mmol/l in women, lymphocytes about 3.5–4 mmol/l) [14, 15].

Body Pool and Losses

Vitamin C is accumulated by almost all human tissues. Higher concentrations (per 100 g wet tissue) are found in the pituitary glands (40–50 mg), the adrenal glands (30–40 mg), the eye lens (25–31 mg) and the brain (13–15 mg) than in the plasma (up to 1 mg), saliva (0.07–0.09 mg), kidney (5–15 mg) and skeletal muscle tissue (up to 4 mg) [31, 32]. The total body pool of vitamin C varies depending on the intake and can reach 1.5–2.0 g in adult men [10, 33].

Maximum metabolic vitamin C losses are about 40–50 mg/day (approx. 3% of the body pool) as observed from studies with non-smoking men. This refers to a plasma ascorbate concentration of about 45–50 μmol/l with a total body pool of about 1.5 g [10, 34–36]. Absolute values for metabolic losses in women are not available. At the same vitamin C intake, smokers have greater metabolic losses than non-smokers due to increased oxidative stress [10, 25, 26, 37].

Vitamin C that is not absorbed by the intestine is partially metabolised to organic acids and carbon dioxide by the microbiota [38] and excreted via faeces [39]. Ascorbic acid and its metabolites like oxalic acid, L-threonic acid and L-xylose are mainly excreted in the urine. Renal excretion rises with increasing plasma concentrations or vitamin C intake levels, respectively, due to saturation of renal tubular reabsorption [14, 15, 18, 40]. At a vitamin C intake of 100 mg/day, about 25% of the vitamin C intake is excreted in the urine [14, 26]. Excretion is strongly increased if the plasma concentration is between 45 and 60 μmol/l [10, 36, 37, 41, 42]; therefore, proximate saturation of body pools is assumed at a concentration from about 50 μmol/l onwards [26].

Urinary Ascorbic Acid

Urinary ascorbic acid concentration reflects recent intakes of vitamin C [15, 43, 44]. In subjects on a vitamin C-deficient diet, urinary excretion declines rapidly to undetectable values [34, 45]. As mentioned before (see 'Body Pool and Losses'), urinary excretion rises with rising plasma ascorbate concentration or vitamin C intake, respectively [14, 15, 18, 40], with ascorbic acid excreted in urine even at low, not yet deficient, plasma ascorbate concentrations and there is an abrupt rise in excretion at plasma concentrations near saturation [10, 36, 37, 41, 42]. However, the measurement of urinary ascorbic acid is of limited value as a marker for vitamin C status. As stated by others [19, 46, 47], urinary ascorbic acid is insensitive and unreliable due to extremely small differences in urinary concentrations found in individuals with either inadequate or normal intakes.

Bioavailability of Vitamin C

The bioavailability (absorption rate) of vitamin C is 80% or higher at intake levels from 15 to 100 mg/day [14, 36, 48]. The higher the vitamin C intake, the lower the absorption rate [10, 14, 18, 49, 50]; at an intake level of 1,250 mg/day or more, it is less than 50% [13, 14, 36, 51]. The European Food Safety Authority (EFSA) takes a bioavailability of about 80% at an intake of 100 mg vitamin C/day as a basis for deriving the reference values for vitamin C intake [26].

Criteria for Derivation of the Reference Values for Vitamin C Intake

The maintenance of the body pools and of plasma and cellular vitamin C concentrations are considered a criterion for establishing the requirement for vitamin C, assuming that proximate saturation of body pools and plasma concentrations is associated with fulfilling the coenzymatic and antioxidant functions of vitamin C [26, 29].

Biomarkers of the functions of vitamin C, like markers of collagen metabolism, carnitine concentrations in blood or urine, markers of oxidative damage such as lipid peroxidation as well as markers of the function of the immune system are not considered to be suitable criteria for deriving the requirement for vitamin C [25, 26]. Present data on the effect of genotype on plasma ascorbate concentration are insufficient to determine the requirements for vitamin C according to genotype variants [26, 28]. Data from studies on the association between vitamin C intake or plasma ascorbate concentrations, respectively, and endpoints as the concentration of blood lipids, blood pressure, risk, severity and duration of common colds and the occurrence of chronic diseases are also no suitable criteria for deriving the requirement for vitamin C [26] (see 'Reference Values for Vitamin C Intake').

Reference Values for Vitamin C Intake

Adults Under 65 Years of Age

In line with the EFSA [26], the average vitamin C requirement in healthy adults is considered to be the vitamin C amount that compensates for the metabolic losses of vitamin C and ensures a fasting ascorbate plasma level of 50 μmol/l.

Based on the present data from studies with non-smoking men, metabolic losses of 50 mg/day are assumed

Table 2. Calculation of the recommended intake of vitamin C for adults

	Average requirement for vitamin C[a, b], mg/day	Coefficient of variation 10% (addition of 20%), mg/day	Recommended intake of vitamin C (rounded), mg/day
Men	50/(80–25)/100) = 90.91	109.09	110
Women	90.91 × (60.0/70.7) = 77.15	92.58	95

[a] $\text{Requirement}_{\text{men (mg/day)}} = \text{metabolic losses}_{\text{(mg/day)}}/((\text{absorption}_{\text{(\% of intake)}} - \text{urinary excretion}_{\text{(\% of intake)}})/100)$.
[b] $\text{Requirement}_{\text{women (mg/day)}} = \text{requirement}_{\text{men}} \times (\text{body weight}_{\text{women}}/\text{body weight}_{\text{men}})$; reference body weight: men 70.7 kg, women 60.0 kg [1].

as well as an absorption rate of 80% and an urinary excretion of 25% of the vitamin C intake. Taking this into account, the calculated average requirement in men is 91 mg/day. Considering a coefficient of variation of 10% (addition of 20%), a recommended intake of about 110 mg/day for men is derived (table 2).

As data on metabolic losses in women are not available, the vitamin C requirement in women is extrapolated from the requirement in men and in relation to their body weight, because body weight is considered to be an essential factor for gender-related differences in the pharmacokinetics of vitamin C. Taking into account their reference body weight, the average requirement in women is 77 mg/day. Assuming a coefficient of variation of 10% (addition of 20%), the recommended intake for women is about 95 mg/day (table 2).

With intake levels according to the recommended intake for adults, the desirable plasma concentration of >50 μmol/l and saturation of immunocompetent cells is achieved [14].

Adults Above 65 Years of Age

So far, pharmacokinetic studies with elderly people or persons with infection, inflammation or other diseases have not been conducted. There are no significant data on deriving other reference values for older adults in comparison with younger adults.

At medium vitamin C intake, no differences regarding the absorption or the metabolism of older compared with younger adults are known. Lower blood concentrations of vitamin C in elderly people may, for example, be due to insufficient intake, chronic diseases or other factors like permanent medication, but not to an effect of aging itself [25].

Thus, the reference values for younger adults are applied to adults above 65 years – 110 mg/day for men and 95 mg/day for women (table 1).

Smokers

As described earlier, smokers have higher metabolic losses and lower plasma levels of vitamin C than nonsmokers. If smokers stop smoking, the vitamin C plasma concentration increases [52].

Kallner et al. [37] compared the effect of vitamin C supplementation in 17 healthy smokers (men at the age of 21–69 years, >20 cigarettes/day) with the effect in nonsmokers [10]. The results showed that for smokers, a daily intake of at least 140 mg is necessary to achieve adequate plasma concentrations and body pools, while nonsmokers achieve this with 100 mg.

Taking into account the by 40% higher turnover, the reference intake values for male and female smokers are set to 155 mg/day for men and to 135 mg/day for women (table 1).

Infants

In infants, there are no systematic investigations regarding the intake of vitamin C and the resulting vitamin C supply.

Breast milk is considered to be the optimal diet for infants [53, 54]. Vitamin C intake from breast milk in breastfed infants is probably higher than the requirement in infants. The vitamin C concentration in breast milk depends on the mother's vitamin C supply, so it rather reflects the mother's intake than the requirement in the infant [55, 56]. Thus, the concentration in breast milk is not considered to be a suitable parameter for deriving the reference value for infants.

Foods consumed by infants in the second half year of life are often fortified with vitamin C; therefore, current data on the intake are considered to be no appropriate basis for deriving reference values for vitamin C intake [26].

Following the procedure adopted by the Scientific Committee on Food [56] and the EFSA [26, 57], for in-

Table 3. Calculation of the recommended intake of vitamin C for children and adolescents

Age, years	Reference body weight, kg [1]		Average requirement[a], mg/day		Coefficient of variation 10% (addition of 20%), mg/day		Recommended intake (rounded), mg/day
	m	f	m	f	m	f	
1 to under 4	13.9	13.2	17.87	16.97	21.45	20.37	20
4 to under 7	20.2	20.1	25.97	25.85	31.17	31.01	30
7 to under 10	29.3	28.7	37.68	36.90	45.21	44.28	45
10 to under 13	41.0	42.1	52.72	54.13	63.26	64.96	65
13 to under 15	55.5	54.0	71.36	69.44	85.64	83.32	85
15 to under 19	69.2	59.5	88.98	76.51	106.78	91.81	105 m, 90 f

[a] $\text{Requirement}_{\text{children}} = \text{requirement}_{\text{adults}} \times (\text{reference body weight}_{\text{children}}/\text{reference body weight}_{\text{adults}})$; $\text{requirement}_{\text{adults}}$: men 91 mg/day, women 77 mg/day; $\text{reference body weight}_{\text{adults}}$: men 70.7 kg, women 60.0 kg [1].

fants in their first year of life, the reference value (estimated value) is set to 20 mg vitamin C/day, based upon the lowest observed vitamin C intake of infants in the United Kingdom and the United States (23 mg/day) that obviously meets the requirement in infants, and that is three times higher than the amount necessary to prevent scurvy (7 mg/day; table 1).

Children and Adolescents

Regarding children and adolescents, no data for deriving the average requirement are available. Following the procedure adopted by the EFSA [26] and the IOM [25], the vitamin C requirement in this age group is extrapolated from the vitamin C requirement in adults, taking into account the differences regarding reference body weight. Recommended intakes are set assuming a coefficient of variation of 10% (addition of 20% to the average requirement; table 3). When using the age groups and reference body weights the D-A-CH reference values are based upon the recommended intake for 1- to under 4-year-olds 20 mg, for 4- to under 7-year-olds 30 mg, for 7- to under 10-year-olds 45 mg, for 10- to under 13-year-olds 65 mg and for 13- to under 15-year-olds 85 mg/day. The recommended intake at the age of 15 to under 19 years is 105 mg/day for male adolescents and 90 mg/day for female adolescents (table 1).

Pregnancy

In pregnant women, haemodilution (higher percentage increase of plasma volume than of erythrocyte volume) [23] and transfer of vitamin C to the foetus [58] lead to a decreased plasma ascorbate concentration and a higher requirement for vitamin C. However, convincing data on the quantitative determination of the requirement in pregnant women or the amount transferred to the foetus are not available.

Irwin and Hutchins [11] summarised six publications from the 1930s to the 1950s that indicate that 67–100 mg up to 200 mg/day is an adequate intake in pregnant women. Olson and Hodges [59] concluded from estimates that for compensation of maternal losses during pregnancy, intake should be increased during the second and third trimesters of pregnancy by 5 and 10 mg/day, respectively. Using these estimates and due to the vitamin C amount of about 7 mg/day that is necessary to prevent scurvy in the infant [60–63], from the fourth month of pregnancy onwards, a 10 mg higher recommended intake in comparison to the requirement in non-pregnant women is derived. Assuming a coefficient of variation of 10% (addition of 20% to the average requirement), the reference value for the intake of pregnant women from the fourth month on is set to 105 mg/day (table 1).

Lactation

The reference value for the intake of vitamin C for lactating women is derived on the basis of the estimated value for infants (20 mg vitamin C/day). At an absorption rate of 80%, about 25 mg vitamin C/day are sufficient to compensate for the amount that is transferred with breast milk when feeding the infant. Therefore, the average requirement in lactating women is 25 mg/day higher than that in non-lactating women. Assuming a coefficient of variation of 10% (addition of 20%), this results in a reference value for the intake that is about 30 mg/day higher than in non-lactating women. Therefore, the recommended intake of vitamin C for lactating women is

125 mg/day (table 1). Considering the estimated vitamin C amount secreted with breast milk while deriving reference values would lead to higher values than probably needed (see 'Infants').

Ensuring a Sufficient Vitamin C Supply

It is possible to achieve a sufficient vitamin C supply by consuming foods that naturally contain the vitamin. A diet rich in vegetables and fruits, according to the food-related recommendations for a wholesome diet [64], provides plenty of vitamin C.

Vegetables and fruits and products made from them such as juices and smoothies are the best sources of vitamin C. For example, foods with particularly high content of vitamin C, containing more than 100 mg/100 g, are buckthorn berries and juice made therefrom, sweet pepper, black current and parsley. However, citrus fruits, potatoes, cabbage, spinach and tomatoes are relevant for the supply of vitamin C due to their high vitamin C content and the quantity that is consumed [65].

Vitamin C is an additive (antioxidant, E300 to E304, E315 and E316) in many processed foods such as meat and sausage products, and so these foods also contribute to the vitamin C supply. Foods that are fortified with vitamin C are commercially available as well. Fortified foods and nutritional supplements are not necessary to ensure a sufficient vitamin C supply.

Preventive Aspects

Oxidative damage to cells and molecules is associated with the development of a number of degenerative chronic diseases. The antioxidative efficacy of vitamin C in the body leads to the hypothesis that vitamin C can affect the occurrence, course and mortality of such diseases. It is also being discussed whether vitamin C strengthens the immune system. In the following, the current available data on vitamin C in association with health-related aspects are outlined using existing meta-analyses or systematic reviews.

In the past, data from observational studies led to the conclusion that a diet rich in vitamin C (plenty of vegetables and fruits) may contribute to the prevention of cardiovascular diseases and some kinds of cancer. However, results from randomised controlled intervention studies (vitamin C supplementation) could not confirm this [25, 26], which suggests that the benefit of a diet rich in vegetables and fruits is not solely caused by the associated intake of a single nutrient such as vitamin C [66, 67].

Regarding cancer and mortality, comprehensive data are available. There is no association with intake or vitamin C supply, respectively [26, 68–73].

There are also many studies available on the relationship between vitamin C intake or supply, respectively, and eye diseases, but they are not consistent or not sufficiently specific [26]. Cochrane reviews of randomised controlled studies on supplementation of vitamin C alone or in combination with other antioxidants conclude that there are no effects on the prevention or course of eye diseases [74–76].

On the basis of a comprehensive review of the literature published between 1991 and 2011 [77], the EFSA [26] has described inconsistent associations between vitamin C intake and/or plasma ascorbate concentrations and bone density as well as the risk of diabetes, Parkinson's disease, Alzheimer's disease, dementia, preterm delivery, breathing difficulties and eczema in the first 2 years of life, medulloblastoma during childhood, hearing loss, periodontal disease and multiple sclerosis. Due to the low number of available studies regarding these endpoints, it is not possible to draw conclusions on the supposed role of vitamin C in the pathogenesis of these diseases [26].

Supplementation of vitamin C during pregnancy for the prevention of pregnancy complications or promotion of the mother's and the child's health is not justified on the basis of the available scientific data [78–80].

In total, intervention studies on the effect of preventive vitamin C supplementation with ≥200 mg/day showed no effect on the incidence of common colds in the general public. However, in a subgroup including marathon runners, skiers and soldiers under subarctic conditions, the risk was reduced by about 50%. When vitamin C was taken prophylactically, the duration of common colds was reduced by 8% in adults and by 14% in children. The severity of the cold was reduced too. The lack of effect of vitamin C supplementation on the incidence of common cold in the general public suggests that routine high-dose prophylaxis is not justified. However, it may be justified for persons under extreme physical strain or in a very cold environment [81]. The EFSA notes about this Cochrane review that common colds were self-diagnosed by the subjects in most of the respective trials, and that no clear criteria were specified to assess either the severity or the duration of a common cold episode [26].

The current data indicate that no preventive effects are to be expected from supplementation of vitamin C in the general public.

References

1 Deutsche Gesellschaft für Ernährung, Österreichische Gesellschaft für Ernährung, Schweizerische Gesellschaft für Ernährung (eds): Referenzwerte für die Nährstoffzufuhr, ed 2. Bonn, 2015.
2 German Nutrition Society: New reference values for vitamin D. Ann Nutr Metab 2012; 60:241–246.
3 German Nutrition Society: New reference values for calcium. Ann Nutr Metab 2013;63: 186–192.
4 Krawinkel MB, Strohm D, Weissenborn A, Watzl B, Eichholzer M, Bärlocher K, Elmadfa I, Leschik-Bonnet E, Heseker H: Revised D-A-CH intake recommendations for folate: how much is needed? Eur J Clin Nutr 2014;68: 719–723.
5 Mandl J, Szarka A, Bánhegyi G: Vitamin C: update on physiology and pharmacology. Br J Pharmacol 2009;157:1097–1110.
6 Johnston CS, Steinberg FM, Rucker RB: Ascorbic acid; in Zempleni J, Rucker RB, McCormick DB, Suttie JW (eds): Handbook of Vitamins, ed 4. Boca Raton, Taylor & Francis, 2007, pp 489–520.
7 Carr AC, Frei B: Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr 1999;69:1086–1107.
8 Sram RJ, Binkova B, Rossner P Jr: Vitamin C for DNA damage prevention. Mutat Res 2012; 733:39–49.
9 Sauberlich HE: Human requirements and needs. Vitamin C status: methods and findings. Ann N Y Acad Sci 1975;258:438–450.
10 Kallner A, Hartmann D, Hornig D: Steady-state turnover and body pool of ascorbic acid in man. Am J Clin Nutr 1979;32:530–539.
11 Irwin MI, Hutchins BK: A conspectus of research on vitamin C requirements of man. J Nutr 1976;106:821–879.
12 Polidori MC, Mecocci P, Levine M, Frei B: Short-term and long-term vitamin C supplementation in humans dose-dependently increases the resistance of plasma to ex vivo lipid peroxidation. Arch Biochem Biophys 2004; 423:109–115.
13 Levine M, Padayatty SJ: Vitamin C; in Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR (eds): Modern Nutrition in Health and Disease, ed 11. Philadelphia, Lippincott Williams & Wilkins, 2014, pp 399–415.
14 Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, Dhariwal KR, Park JB, Lazarev A, Graumlich JF, King J, Cantilena LR: Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A 1996;93:3704–3709.
15 Levine M, Wang Y, Padayatty SJ, Morrow J: A new recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci U S A 2001;98:9842–9846.
16 Levine M, Padayatty SJ, Espey MG: Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries. Adv Nutr 2011;2:78–88.
17 Rumsey SC, Levine M: Absorption, transport, and disposition of ascorbic acid in humans. J Nutr Biochem 1998;9:116–130.
18 Blanchard J, Tozer TN, Rowland M: Pharmacokinetic perspectives on megadoses of ascorbic acid. Am J Clin Nutr 1997;66:1165–1171.
19 Harvey LJ, Collings R, Casgrain A, Fairweather-Tait SJ: Best practice guidelines: biomarkers of status/exposure. EURRECA, 2012. www.eurreca.org/everyone/8647/5/0/32 (accessed November 12, 2014).
20 Hampl JS, Taylor CA, Johnston CS: Vitamin C deficiency and depletion in the United States: the third national health and nutrition examination survey, 1988 to 1994. Am J Public Health 2004;94:870–875.
21 Giraud DW, Martin HD, Driskell JA: Plasma and dietary vitamin C and E levels of tobacco chewers, smokers, and nonusers. J Am Diet Assoc 1995;95:798–800.
22 Brubacher D, Moser U, Jordan P: Vitamin C concentrations in plasma as a function of intake: a meta-analysis. Int J Vitam Nutr Res 2000;70:226–237.
23 Morse EH, Clarke RP, Keyser DE, Merrow SB, Bee DE: Comparison of the nutritional status of pregnant adolescents with adult pregnant women. I. Biochemical findings. Am J Clin Nutr 1975;28:1000–1013.
24 Scaife AR, McNeill G, Campbell DM, Martindale S, Devereux G, Seaton A: Maternal intake of antioxidant vitamins in pregnancy in relation to maternal and fetal plasma levels at delivery. Br J Nutr 2006;95:771–778.
25 Institute of Medicine: Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, National Academies Press, 2000.
26 European Food Safety Authority: Scientific opinion on dietary reference values for vitamin C. EFSA J 2013;11:3418.
27 Dehghan M, Akhtar-Danesh N, McMillan CR, Thabane L: Is plasma vitamin C an appropriate biomarker of vitamin C intake? A systematic review and meta-analysis. Nutr J 2007;6:41.
28 Michels AJ, Hagen TM, Frei B: Human genetic variation influences vitamin C homeostasis by altering vitamin C transport and antioxidant enzyme function. Annu Rev Nutr 2013;33:45–70.
29 Levine M, Rumsey SC, Daruwala R, Park JB, Wang Y: Criteria and recommendations for vitamin C intake. JAMA 1999;281:1415–1423.
30 Lukaski HC: Vitamin and mineral status: effects on physical performance. Nutrition 2004;20:632–644.
31 Hornig D: Distribution of ascorbic acid, metabolites and analogues in man and animals. Ann N Y Acad Sci 1975;258:103–118.
32 Carr AC, Bozonet SM, Pullar JM, Simcock JW, Vissers MC: Human skeletal muscle ascorbate is highly responsive to changes in vitamin C intake and plasma concentrations. Am J Clin Nutr 2013;97:800–807.
33 Kallner A: Requirement for vitamin C based on metabolic studies. Ann N Y Acad Sci 1987; 498:418–423.
34 Baker EM, Hodges RE, Hood J, Sauberlich HE, March SC: Metabolism of ascorbic-1-14C acid in experimental human scurvy. Am J Clin Nutr 1969;22:549–558.
35 Baker EM, Hodges RE, Hood J, Sauberlich HE, March SC, Canham JE: Metabolism of 14C- and 3H-labeled L-ascorbic acid in human scurvy 1971;24:444–454.
36 Graumlich JF, Ludden TM, Conry-Cantilena C, Cantilena LR Jr, Wang Y, Levine M: Pharmacokinetic model of ascorbic acid in healthy male volunteers during depletion and repletion. Pharm Res 1997;14:1133–1139.
37 Kallner AB, Hartmann D, Hornig DH: On the requirements of ascorbic acid in man: steady-state turnover and body pool in smokers. Am J Clin Nutr 1981;34:1347–1355.
38 Kallner A, Hornig D, Pellikka R: Formation of carbon dioxide from ascorbate in man. Am J Clin Nutr 1985;41:609–613.
39 Gibney MJ, Lanham-New SA, Cassidy A, Vorster HH (eds): Introduction to human nutrition, ed 2. The Nutrition Society Textbook Series. Chichester, Wiley-Blackwell, 2009.
40 Uchida E, Kondo Y, Amano A, Aizawa S, Hanamura T, Aoki H, Nagamine K, Koizumi T, Maruyama N, Ishigami A: Absorption and excretion of ascorbic acid alone and in acerola (Malpighia emarginata) juice: comparison in healthy Japanese subjects. Biol Pharm Bull 2011;34:1744–1747.
41 Friedman GJ, Sherry S, Ralli EP: The mechanism of the excretion of vitamin C by the human kidney at low and normal plasma levels of ascorbic acid. J Clin Invest 1940;19:685–689.
42 Carr AC, Pullar JM, Moran S, Vissers MC: Bioavailability of vitamin C from kiwifruit in non-smoking males: determination of 'healthy' and 'optimal' intakes. J Nutr Sci 2012;1:e14.
43 Fukuwatari T, Shibata K: Urinary water-soluble vitamins and their metabolite contents as nutritional markers for evaluating vitamin intakes in young Japanese women. J Nutr Sci Vitaminol (Tokyo) 2008;54:223–229.
44 Tsuji T, Fukuwatari T, Sasaki S, Shibata K: Twenty-four-hour urinary water-soluble vitamin levels correlate with their intakes in free-living Japanese university students. Eur J Clin Nutr 2010;64:800–807.
45 Hodges RE, Baker EM, Hood J, Sauberlich HE, March SC: Experimental scurvy in man. Am J Clin Nutr 1969;22:535–548.
46 Sauberlich HE: Laboratory tests for the assessment of nutritional status, 2. Auflage. CRC series in modern nutrition. Boca Raton, CRC Press, 1999.

47 Benzie IF: Vitamin C: prospective functional markers for defining optimal nutritional status. Proc Nutr Soc 1999;58:469–476.
48 Kallner A, Hartmann D, Hornig D: On the absorption of ascorbic acid in man. Int J Vitam Nutr Res 1977;47:383–388.
49 Hornig D, Vuilleumier JP, Hartmann D: Absorption of large, single, oral intakes of ascorbic acid. Int J Vitam Nutr Res 1980;50:309–314.
50 Melethil S, Mason WD, Chian-Jo C: Dose-dependent absorption and excretion of vitamin C in humans. Int J Pharm 1986;31:83–89.
51 Kübler W, Gehler J: Zur Kinetik der enteralen Ascorbinsäure-Resorption. Ein Beitrag zur Berechnung nicht dosisproportionierter Resorptions-vorgänge. Int Z Vitaminforsch 1970; 40:442–453.
52 Polidori MC, Mecocci P, Stahl W, Sies H: Cigarette smoking cessation increases plasma levels of several antioxidant micronutrients and improves resistance towards oxidative challenge. Br J Nutr 2003;90:147–150.
53 Butte NF, Lopez-Alarcon MG, Garza C: Nutrient adequacy of exclusive breastfeeding for the term infant during the first six months of life. 2002. www.who.int/nutrition/publications/infantfeeding/nut_adequacy_of_exc_bfeeding_eng.pdf (accessed June 25, 2013).
54 Bührer C, Genzel-Boroviczény O, Jochum F, Kauth T, Kersting M, Koletzko B, Mihatsch W, Przyrembel H, Reinehr T, Zimmer P: Ernährung gesunder Säuglinge. Monatsschr Kinderheilkd 2014;162:527–538.
55 World Health Organization, Food and Agriculture Organization: Vitamin and Mineral Requirements in Human Nutrition, ed 2. World Health Organization, 2004.
56 Scientific Committe on Food: Nutrient and Energy Intakes for the European Community: Reports of the Scientific Committee for Food (Thirty-First Series). Luxemburg, 1993.
57 European Food Safety Authority: Scientific opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. EFSA J 2013;11:3408.
58 Choi JL, Rose RC: Transport and metabolism of ascorbic acid in human placenta. Am J Physiol 1989;257:C110–C113.
59 Olson JA, Hodges RE: Recommended dietary intakes (RDI) of vitamin C in humans. Am J Clin Nutr 1987;45:693–703.
60 van Eekelen M: The occurrence of vitamin C in foods. Proc Nutr Soc 1953;12:228–232.
61 Goldsmith GA: Human requirements for vitamin C and its use in clinical medicine. Ann N Y Acad Sci 1961;92:230–245.
62 Rajalakshmi R, Deodhar AD, Ramakrishnan CV: Vitamin C secretion in lactation. Acta Paediatr Scand 1965;54:375–382.
63 Bischoff H, Müller K: Natürliches und synthetisches Vitamin C in der Säuglingsernährung. Dtsch med Wochenschr 1942;68: 1257.
64 Oberritter H, Schäbethal K, Rüsten A von, Boeing H: The DGE nutrition circle – presentation and basis of the food-related recommendations from the German Nutrition Society (DGE). Ernaehrungs Umschau Int 2013; 60:24–29.
65 Deutsche Gesellschaft für Ernährung: DGExpert, Version 1.5.4 (BLS 3.02). Bonn, 2014.
66 Drake V, Frei B: Vitamin C in human disease prevention; in Herrmann W, Obeid R (eds): Vitamins in the Prevention of Human Diseases. Berlin, De Gruyter, 2011, pp 347–362.
67 Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, Leschik-Bonnet E, Müller MJ, Oberritter H, Schulze M, Stehle P, Watzl B: Critical review: vegetables and fruit in the prevention of chronic diseases. Eur J Nutr 2012;51:637–663.
68 Cortés-Jofré M, Rueda JR, Corsini-Muñoz G, Fonseca-Cortés C, Caraballoso M, Bonfill Cosp X: Drugs for preventing lung cancer in healthy people. Cochrane Database Syst Rev 2012;10:CD002141.
69 Bjelakovic G, Nikolova D, Simonetti RG, Gluud C: Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database Syst Rev 2008;3:CD004183.
70 Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev 2012;3: CD007176.
71 Papaioannou D, Cooper KL, Carroll C, Hind D, Squires H, Tappenden P, Logan RF: Antioxidants in the chemoprevention of colorectal cancer and colorectal adenomas in the general population: a systematic review and meta-analysis. Colorectal Dis 2011;13:1085–1099.
72 Jiang L, Yang KH, Tian JH, Guan QL, Yao N, Cao N, Mi DH, Wu J, Ma B, Yang SH: Efficacy of antioxidant vitamins and selenium supplement in prostate cancer prevention: a meta-analysis of randomized controlled trials. Nutr Cancer 2010;62:719–727.
73 Stratton J, Godwin M: The effect of supplemental vitamins and minerals on the development of prostate cancer: a systematic review and meta-analysis. Fam Pract 2011;28:243–252.
74 Mathew MC, Ervin AM, Tao J, Davis RM: Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. Cochrane Database Syst Rev 2012;6:CD004567.
75 Evans JR, Lawrenson JG: Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. Cochrane Database Syst Rev 2012;6:CD000253.
76 Evans JR, Lawrenson JG: Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev 2012; 11:CD000254.
77 Heinonen M, Kärkkäinen M, Riuttamäki M, Piironen V, Lampi A, Ollilainen V, Lamberg-Allardt C: Literature search and review related to specific preparatory work in the establishment of dietary reference values. 2012. www.efsa.europa.eu/de/supporting/doc/256e.pdf (accessed October 31, 2014).
78 Rumbold A, Middleton P, Pan N, Crowther CA: Vitamin supplementation for preventing miscarriage. Cochrane Database Syst Rev 2011;1:CD004073.
79 Dror DK, Allen LH: Interventions with vitamins B_6, B_{12} and C in pregnancy. Paediatr Perinat Epidemiol 2012;26(suppl 1):55–74.
80 Conde-Agudelo A, Romero R, Kusanovic JP, Hassan SS: Supplementation with vitamins C and E during pregnancy for the prevention of preeclampsia and other adverse maternal and perinatal outcomes: a systematic review and metaanalysis. Am J Obstet Gynecol 2011;204: 503.e1–e12.
81 Hemilä H, Chalker E: Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013;1:CD000980.