Maximum levels for the addition of folic acid to foods including food supplements

The accompanying main opinion "**Updated recommended maximum levels for the addition of vitamins and minerals to food supplements and conventional foods**" can be found here: https://www.bfr.bund.de/cm/349/updated-recommended-maximum-levels-for-the-addition-of-vitamins-and-minerals-to-food-supplements-and-conventional-foods.pdf

1 Results

The German Federal Institute for Risk Assessment (BfR) recommends for folic acid a maximum level of 200 micrograms (µg) per daily recommended dose of a food supplement (Table 1).

Notwithstanding this, supplementation of 400 µg folic acid per day for women of childbearing age and pregnant women in the first trimester is still considered the most appropriate measure for the reduction of risk of neural tube defects (NRD) and is explicitly recommended. For products with folic acid dosages at this level, clear labelling and targeted communication measures are essential.

Table 1: Proposed maximum levels

Food category	Maximum levels
Food supplements (per daily recommended dose of an individual product)	200 µg
Food supplements for NRD risk reduction (per daily recommended dose of an individual product)	400 µg

For the fortification of conventional foods with folic acid, the derivation based on the assumption of a ‘saturated’ market of fortified foods resulted in maximum levels which, according to Regulation (EU) No 1169/2011, would partly have to be classified as insignificant and thus would not be allowed to be claimed according to Regulation (EC) No 1924/2006. In view of this, the BfR proposes the following options for setting maximum levels for the fortification of conventional foods (excluding food ingredients such as table salt and flour) with folic acid:

Option 1: Under the assumption that the market of fortified foods is and will be only partially saturated, a maximum level of 80 µg/100 grams (g) could be proposed for solid food and of 20 µg/100 millilitres (ml) for beverages. The level of protection would be lower than under the assumption of a saturated market.

Option 2: Setting maximum levels corresponding to 15 % and 7.5 % of the reference value for nutrition labelling, which is 200 µg for folic acid. This means that solid foods could be fortified with 30 µg/100 g and beverages with 15 µg/100 ml of folic acid.

Option 3: Restrict the addition of folic acid to the food groups "breakfast cereals", "dairy products" and "juices and soft drinks".
Under these conditions, breakfast cereals and dairy products could be fortified with up to 50 µg/100 g or ml and juices and soft drinks with 15 µg/100 ml.

Option 4: Restricting the addition of folic acid to solid foods with a maximum level of 80 µg/100 g.

It is noted here that the current use of table salt fortified with folic acid (100 µg folic acid per g) has been included in the above options. In contrast, fortification of flour and processed foods made with it, as implemented for example in the USA and Canada since the late 1990's to reduce the risk of NRD, was not taken into account in the derivation of maximum levels. If mandatory or voluntary extensive fortification of flour (and products made with it) with folic acid is to be introduced in Germany, the BfR is of the view that updates of the available model calculations (BfR, 2005; MRI, 2011) with regard to suitable dosages and restrictions of food fortification with folic acid would be necessary. In this context, the BfR refers to its risk-benefit assessment of a nationwide fortification of flour with folic acid (BfR, 2017), in which it was stated that the fortification of flour with folic acid, in addition to fortified products already available on the market, would increase the risk of exceedances of the UL and thus the risk of adverse effects and therefore cannot be recommended at present.

2 Rationale

2.1 Tolerable Upper Intake Level[1] (UL) and Dietary Reference Value

In accordance with Regulation (EC) No 1170/2009 of 30 November 2009, both pteroylmonoglutamate and calcium L-methylfolate may be used as sources of folate in food supplements and for fortification of conventional foods.

The bioavailability of calcium L-methylfolate is comparable to that of pteroylmonoglutamate; however, calcium L-methylfolate may enter directly into the folate metabolism after uptake into the organism, whereas folic acid must first be converted in several steps into the bioactive form 5-methyltetrahydrofolate (5-methyl-THF). Also, the intake of calcium L-methylfolate leads to higher red blood cell folate concentrations (Lamers et al., 2006; Pietrzik et al., 2001).

In 2000, the former Scientific Committee on Food (SCF) of the European Commission derived a UL for folic acid (pteroylmonoglutamate) of 1 milligram per day (mg/day) for adults and 0.8 mg/day for adolescents aged 15 to 17 years. The endpoint for adverse health effects was based on the possible 'masking' of a vitamin B_{12} deficiency from folic acid intakes of 5 mg/day upwards. Applying an uncertainty factor of 5 resulted in a UL of 1 mg/day. The UL applies exclusively to synthetic folic acid (SCF, 2000 cited in: EFSA, 2006; Table 2). In 2004, the Panel on Food Additives and Nutrient Sources Added to Food (ANS) of the European Food Safety Authority (EFSA) approved calcium L-methylfolate as another source of folate and concluded that this compound could also be used in foods for the general population at the level of the UL derived for folic acid without health concern (EFSA, 2004).

The D-A-CH Societies[2] have derived a dietary reference value of folate equivalents (DFE) of 300 µg/day for adolescents ≥ 13 years and adults. For pregnant and lactating women, intakes of 550 and 450 µg DFE per day, respectively, were recommended. Furthermore, women who wish to or might become pregnant should supplement 400 µg/day folic acid in addition to a folate-rich diet in order to reduce the risk of neural tube defects in the offspring (D-A-CH, 2015; Table 2).

[1] Tolerable Upper Intake Level = Maximum level of total chronic daily intake of a nutrient (from all sources) considered to be unlikely to pose a risk of adverse health effects to humans.

[2] German-Austrian-Swiss Nutrition Societies

EFSA has derived a dietary reference value of 330 µg DFE per day for all age groups ≥ 15 years and for pregnant and lactating women 600 and 500 µg DFE per day, respectively (EFSA, 2014; Table 2).

Table 2: Dietary reference values and UL

Age groups	Dietary reference values		UL**
	D-A-CH (2018)	EFSA (2014)	
	µg DFE*/day		µg/day
4 to < 7 years	140	140	300
7 to < 10 years	180	200 (7 – 10 J.)	400
10 to < 13 years	240	270 (11 – 14 J.)	600
13 to < 15 years	300		600
15 to < 19 years***	300	330	800
Adults***	300	330	1,000
Pregnant women***	550	600****	1,000
Lactating women	450	500	1,000

* 1 µg folate equivalent (DFE) = 1 µg dietary folate = 0.5 µg synthetic folic acid (when taken on an empty stomach) = 0.6 µg synthetic folic acid (when taken with foods)

** The UL applies only to synthetic folic acid.

*** Women who wish to or might become pregnant should take 400 µg of synthetic folic acid per day as a supplement in addition to a folate-rich diet to reduce the risk of neural tube defects (NRD). Supplementation should be started at least four weeks before the commencement of pregnancy and maintained until the end of the first trimester.

**** Adequate Intake (AI)

2.2 Exposure

The analysis of data[3] obtained in the second National Food Consumption Survey (NFCS II) showed that men and women aged 18 years and older had median dietary intakes of between 182 and 214 µg and between 153 and 193 µg DFE per day, respectively, depending on age. In the 95th percentile, the DFE intakes varied age-dependently between 331 and 387 µg for men and between 293 and 320 µg for women (DGE, 2012).

The results of the NFCS II show that the median DFE intake of men and women in all age groups is below the D-A-CH dietary reference value of 300 µg/day. When analysing the intake data, it must be taken into account that within the NFCS II, both the consumption of fortified foods and of (folic acid-fortified) table salt as well as the intake of food supplements could not be (completely) recorded and/or included in the evaluation.

In addition to intake data, the German Health Interview and Examination Survey (DEGS 1), for the first time, determined representative data on biomarkers of folate status (serum and

[3] In contrast to most other micronutrients, intake data for folate equivalents were drawn from 24-hour recall data of the NFCS II, evaluated with the National Food Code (BLS) version 3.02. This was done in order that the model calculations carried out by use of this data base by the Max Rubner-Institute (MRI) could be taken into consideration in the derivation of maximum levels.

red blood cell folate) for the German adult population, which allow a more reliable interpretation of the folate supply situation of the population. The data obtained suggest that about 86 % of adults are adequately supplied with folate (DGE, 2016).

In children, the intake of folate equivalents was determined within the EsKiMo study (nutrition module in KiGGS[4]) conducted by the Robert Koch Institute (RKI) in 2006. According to these data, 6- to 11-year-old boys and girls showed median intakes of 204 and 190 µg folate equivalents per day, respectively and the 95th intake percentiles were at 496 and 365 µg/day, respectively (Mensink et al. 2007). In the 12- to 17-year-olds, the median DFE intakes were 320 µg (male) and 286 µg (female) per day, and in the 95th percentile, 929 µg (male) and 731 µg (female) per day (Mensink et al., 2007). The median intakes of children and adolescents thus meet the reference values derived for the respective age groups (4- to 6-year-olds: 140 µg/day; 7- to 9-year-olds: 180 µg/day; ≥ 13-year-olds: 300 µg/day).

2.3 Maximum levels for folic acid in food supplements and conventional foods

2.3.1 Aspects considered in the derivation of maximum levels

While the results of consumption surveys show that the intake of folate equivalents in all age groups of adults is below the dietary reference value of 300 µg/day, serum and erythrocyte folate concentrations measured in the DEGS 1 study indicate that the adult population in Germany is generally well supplied with folate.

In Germany, there is a large number of folic acid-fortified foods available. According to market analysis conducted by the MRI (with respect to the market situation in the year 2010), the most commonly fortified foods/ food groups are soft drinks and juices, cereals and cereal products, cocoa powder, dairy products, margarine, instant soups, confectionery and foods marketed for athletes (MRI, 2011; Table 3). In addition, some table salt products for household use and some bread baking mixes are fortified with folic acid (Table 3).

Table 3: Folic acid concentrations in fortified foods on the market in Germany (MRI, 2011, complemented by own analyses on bread baking mixes)

Food categories	Folic acid in µg/100 g or µg/100 ml
Beverages (soft drinks and juices)	30 - 245
Breakfast cereals/muesli	170 - 340
Cocoa powder	194 - 286
Dairy products	9 - 82
Margarine	100 – 1,000
Soups (instant products)	18 - 25
Confectionery	47 - 800
Foods for sportspeople and other foods for special nutritional uses	13 - 600
Salt	10,000
Bread mixes	125

[4] German Health Interview and Examination Survey for Children and Adolescents

Model calculations by the MRI (2011) showed that the median intake of adults would reach the dietary reference value of the D-A-CH Societies (at the time of the calculation 400 µg/day) only if they consumed fortified products with high folic acid concentrations instead of conventional unfortified foods. On the other hand, according to the MRI model calculations, up to 5 % of adults would be at risk of exceeding the UL through the consumption of highly fortified foods, with supplement users being particularly affected (MRI, 2011; Martiniak et al., 2015).

In children and adolescents (< 1 to 18 years of age), special analyses of the DONALD study (dietary records from 1990 to 2001) revealed that folic acid-fortified foods contribute, regardless of age and sex, by 50 % to folate intakes from all sources and food supplements (in 15- to 18-year-olds) contribute by 8%, and that folate intakes are about twice as high in those who consume fortified foods than in those who do not consume such foods. The results also suggest that with a high intake of fortified foods (P95), children between two and six years of age to some extent achieve folic acid intakes that are close to or above the UL derived for the respective age groups (BfR, 2005).

In view of results from intervention studies with folic acid supplements as well as with respect to the overall scientific evidence, there is a possibility that folic acid intakes, perhaps even below the UL, could increase the risk for the development or progression of cancer, in particular of the colon and prostate, under certain conditions (e.g.: Cole et al., 2007; Ebbing et al., 2009; Figueiredo et al., 2009). The risk seems to be influenced by several factors such as age, sex, dose, folate status, previous diseases, and gene polymorphisms. Specific risk groups are the elderly, as they are more likely to have precancerous lesions, and populations with certain genetic polymorphisms. In spite of inconsistent data and existing knowledge gaps, the available scientific evidence should be taken seriously and further clarified (NTP, 2015).

The UL of 1 mg/day or of 0.8 mg/day for adolescents 15 to 17 years of age applies to both folic acid and calcium L-methylfolate. Under the condition that food supplements should be of no harm for all consumers ≥ 15 years of age, the derivation of maximum levels is based on the UL for 15- to 17-year-olds.

The intake of folate through the usual diet can be disregarded when deriving maximum levels.

In view of a multiple intake of folic acid from different food supplements (Römer and Heuer, 2017), which cannot be ruled out, an uncertainty factor of 2 is applied in the derivation of maximum levels for food supplements.

If one follows the procedure proposed by the BfR[5], taking into account that folate intake via conventional foods can be disregarded in the derivation of maximum levels, this would result in a total residual amount of 800 µg/day, which can be divided equally between the two categories of food supplements and fortified conventional foods. Consequently, 400 µg of folic acid is available for use in each of the two food categories.

In Germany, folic acid-fortified table salt has been on the market for many years. Due to its use as an ingredient in meal preparation, salt is not comparable with conventional foods. No reliable information is available on the actual use level and consumption of that type of salt in

[5] Residual amount = $UL_{15\text{-to }17\text{-year-olds}}$ - $P95_{\text{diet }15\text{-to }17\text{-year-olds}}$ = 800 µg/day - 0 µg/day = 800 µg/day

the German population, partly because data on the use of table salt at the household level are generally unreliable. However, it is generally estimated that the average amount of salt added in the kitchen or plate at home is 1 to 2 g per person per day (Manz, 1991). Since the use of folic acid-fortified table salt can contribute significantly to folic acid intake, this potential source of folic acid should, in the view of the BfR, be taken into account in the derivation of maximum levels for the fortification of conventional foods.

2.3.2 Maximum levels for folic acid in food supplements

Based on a residual amount available for food supplements of 400 µg/day and taking into account an uncertainty factor of 2, the resultant maximum level is 200 µg per daily recommended dose of a food supplement.

Nevertheless, the supplementation of 400 µg folic acid per day for women of childbearing age and pregnant women in the first trimester is still considered the most appropriate measure to reduce the risk of NRD in newborns and is explicitly recommended. Clear labelling of appropriately dosed products and measures for targeted communication are essential in this context.

2.3.3 Maximum levels for folic acid in conventional foods

As stated above, table salt should in view of the BfR be taken into account as a potential source of significant folic acid intake when deriving maximum levels for fortification of conventional foods. Although the use level and the actual use of that salt are not known, at least an amount of about 70 µg folic acid per day (95th percentile of the NFCS II population) estimated to come from the use of this salt in the model calculations of the MRI (2011) should be included in the derivation of maximum levels. This results in a residual amount$_{FF}$ of 330 µg/day, reduced by 70 µg/day, being available for fortification of conventional foods[6].

Allocating this residual amount to the estimated daily energy intake from fortified foods and assuming that 15 % to a maximum of 30 % of the daily energy is consumed from fortified foods, results in age-dependent maximum levels of between 23 and 110 µg/100 kcal for folic acid in fortified foods (Table 4).

In order to ensure that none of the age groups exceeds the respective age-specific UL, the lowest of the folic acid levels resulting from the calculations are proposed as maximum levels, i.e. 23 µg/100 kcal under the assumption that the market of fortified foods is ‘saturated’ (30 % of the daily energy comes from fortified foods) and 47 µg/100 kcal under the assumption that a smaller part of the fortifiable foods is actually fortified and consumed in this form (15 % of the energy intake comes from fortified foods) (Table 4).

[6] Residual amount$_{FF}$ = Residual amount$_{FF\ incl\ folic\ acid\text{-}salt}$ - P95$_{Folic\ acid\ from\ salt}$= (400 - 70) µg/day = 330 g/day

Table 4: Daily energy intakes (P95) of the population and possible folic acid supplements [µg/100 kcal] assuming that 15 % or 30 % of the ingested energy comes from fortified foods.

Age groups	Energy intake*	Fortification of 15 % of the energy intake		Fortification of 30 % of the energy intake	
		15 % of daily energy intake	Folic acid**	30 % of daily energy intake	Folic acid**
	kcal/day	*kcal*	*µg/100 kcal*	*kcal*	*µg/100 kcal*
4 to 6 years	2,000	300	110	600	55
7 to 9 years	2,400	360	92	720	46
10 to 11 years	2,550	383	86	765	43
12 years	3,900	585	56	1,170	28
13 to < 15 years	3,900	585	56	1,70	28
15 to < 17 years	4,700	705	47	1,410	23
Adults	3,500	525	63	1,050	31

* Data for children up to the age of 17 from EsKiMo and for adults from NFCS II

** Allocation of the residual amount of 330 µg/day to 100 kcal-servings

2.3.3.1 Conversion of energy-based maximum levels into maximum levels per 100 g of solid foods and per 100 ml of beverages

The conversion of the energy-based maximum levels into weight- and volume-based maximum levels was carried out taking into account the average energy densities determined by Schusdziarra et al. (2010) and Bechthold (2014) for solid foods (170 kcal/100 g) and for energy-containing liquids such as juices and soft drinks (45 kcal/100 ml). As shown in Table 5, depending on the baseline value, maximum levels of 40 or 80 µg per 100 g of solid food or 10 or 20 µg per 100 ml of a beverage result (Table 5).

Table 5: Conversion of energy-based to weight and volume-based maximum levels

Folic acid per 100 kcal	Folic acid per 100 g or ml	
	Solid foods (energy density: 170 kcal/100 g)	**Beverages** (energy density: 45 kcal/100 ml)
23 µg	40 µg	10 µg
47 µg	80 µg	20 µg

If an additional criterion in setting maximum levels is that the amount added to a food should be significant in order to be allowed to be claimed in the product labelling in accordance with Regulation (EC) No 1924/2006[7], then according to Regulation (EU) No 1169/2011 at least 15 % of the respective nutrient reference value (NRV) must be contained in solid foods and at least 7.5 % of the respective reference value in beverages per 100 g and 100 ml, respectively.

[7] Conditions for labelling of products with a claim "source of..." or "rich in...", according to EU Regulation 1924/2006 (Health Claim Regulation). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:404:0009:0025:DE:PDF; last accessed 05 March 2021.

For folic acid the NRV is 200 µg. This means that only folic acid levels ≥ 30 µg/100 g or ≥ 15 µg/100 ml would be considered significant. In view of the values given in Table 5, a maximum level of 10 µg/100 ml would thus not be considered significant (Table 5). It would, however, be possible to set the lowest folic acid concentrations classified as significant according to Regulation (EU) No 1169/2011, i.e. 30 µg/100 g for solid foods and 15 µg/100 ml for beverages, as maximum levels for the fortification of conventional foods.
In addition, in cases where the derivation procedure results in insignificant maximum levels, it is proposed to exempt further food (categories) from fortification, apart from those mentioned in Article 4 of Regulation (EC) 1925/2006. For example, the addition of folic acid could be limited to the three food groups currently most frequently fortified: "breakfast cereals", "dairy products" and "juices and soft drinks".[8] Alternatively, juices and soft drinks, whose consumption is difficult to limit and which can lead to very high intakes of folic acid in high consumers, could be excluded from fortification. For the latter two options, maximum levels are derived below.

2.3.3.2 Maximum levels subject to the condition that only certain foods or food groups are fortified with folic acid

a) Restriction of folic acid fortification to "breakfast cereals", "dairy products" and "fruit juices and soft drinks".

According to results from the NFCS II, the consumption of breakfast cereals, dairy products and fruit juices/soft drinks contributes about 25 % of the energy intake in the 95th consumption percentile. Assuming that all of the foods consumed from the three groups were fortified with folic acid *(worst case*), the residual folic acid amount$_{FF}$ available for fortification of conventional foods (330 µg/day) could thus be allocated to 25 % of the daily energy intake (Table 6).

Table 6: Daily energy intakes (P95) of the population and possible folic acid supplements [µg/100 kcal] assuming that 25 % of the ingested energy comes from fortified foods

Age groups	Energy intake*	25 % of daily energy intake	Folic acid**
	kcal/day	*kcal*	*µg/100 kcal*
4 to 6 years	2,000	500	66
7 to 9 years	2,400	600	55
10 to 11 years	2,550	638	52
12 years	3,900	975	34
13 to < 15 years	3,900	975	34
15 to < 17 years	4,700	1,175	28
Adults	3,500	875	38

* Data for children up to the age of 17 from EsKiMo and for adults from NFCS II

** Allocation of the residual amount of 330 µg/day to 100 kcal-servings

If the lowest folic acid value (28 µg/100 kcal; rounded up to 30 µg/100 kcal) from Table 6 is taken and converted into folic acid levels per 100 g or 100 ml (see 2.3.3.1), the following

[8] According to NFCS II, women and men drank an average of 300 and 500 ml/day, respectively, of soft drinks, fruit juice drinks, and fruit and vegetable juices; the 95th consumption percentiles were approximately 500 to 1200 ml/day for soft drinks alone.

maximum levels result for the three food groups considered, which can be regarded as significant amounts in accordance with Regulation (EU) No 1169/2011:

- breakfast cereals and dairy products: 50 µg/100 g or ml
- juices and soft drinks: 15 µg/100 ml

b) Restriction of folic acid fortification to solid foods (prohibition of fortification of "juices and soft drinks")

If folic acid fortification were restricted to solid foods, the available residual amount$_{FF}$ of 330 µg/day could be allocated to 15 % of the daily energy from fortifiable solid foods, based on the assumption that the estimated daily energy contribution of fruit juices and soft drinks is about 15 %. Under this condition, the maximum amount would be 80 µg/100 g (see Tables 4 and 5, assuming that 15 % of the daily energy comes from fortified foods).

2.3.3.3 Folic acid supplementation and nationwide fortification of flour with the aim of reducing the risk of neural tube defects in newborns

Due to the observed association between increased periconceptional folic acid intakes and a reduced risk of neural tube defects (NRD), it has been recommended since about the mid-1990s in Germany and many other countries around the world that women who wish to or might become pregnant supplement 400 µg of folic acid per day in addition to a folate-rich diet.

In view of the difficulties observed, also in other countries, in implementing this recommendation, the USA and Canada began at the end of the 1990s to fortify flour with folic acid in order to reduce the risk of NRD. In the meantime, flour or grains and products made from them are fortified with folic acid in about 80 countries worldwide.

In Germany and other EU member states, too, the benefits and risks of nationwide flour fortification with folic acid have since been repeatedly discussed. The BfR commented on this in detail in 2005 and 2017 (BfR, 2005; BfR, 2017) and found that

- it is difficult to assess the benefit of a flour fortification measure for Germany on the basis of the available data;
- the population as a whole, most of whom are well supplied with folate, would not benefit from widespread flour fortification, but - in view of other foods currently fortified with folic acid, including table salt and food supplements - the risk of high folic acid intakes and thus of negative health effects would increase.

Therefore, the BfR is of the opinion that, when considering a mandatory or voluntary wide-ranging flour fortification measure, updates of the existing model calculations (BfR, 2005; MRI, 2011) on appropriate dosages and on restrictions of other food fortification with folic acid would be necessary.

Under the current conditions of widespread fortification of conventional foods and table salt with folic acid, the BfR advocates increased attention to information campaigns for the targeted increase of folic acid intake in women of childbearing age and pregnant women in the first trimester by means of food supplements containing 400 µg folic acid per daily dose.

Further information on the BfR website on vitamins

A-Z Index on vitamins: https://www.bfr.bund.de/en/a-z_index/vitamins-130216.html

Topic page on the assessment of vitamins and minerals in foods: https://www.bfr.bund.de/en/vitamins_and_minerals-54417.html

"Opinions-App" of the BfR

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the German federal government and German federal states ("Laender") on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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