

**Arguments against capping the content of folic acid in food supplements at
200 micrograms per daily dose
Authored by The Health Supplements Information Service**

The Food Standards Agency (FSA) has proposed a maximum daily dose (MDD) of 200mcg folic acid from supplements based on the UK Reference Nutrient Intake (RNI) for the general population except for women of childbearing age. Supplements aimed at women of childbearing age (19-49 years) are proposed to have MDD of 400 mcg

What is folic acid?

Folic acid (pteroylglutamic acid) is an essential water-soluble vitamin. It is one of a family of chemically similar substances known as folates, which fall within the vitamin B group. Folic acid is the most stable and bioavailable form of folate and the form used most often in food supplements and food fortification.

Folates are also found naturally in food (eg, fresh, green leafy vegetables such as spinach, cabbage, broccoli and sprouts, and also legumes, nuts and organ meats). Folates have a poorer bioavailability than folic acid, 50-66% compared with 85-100% respectively. In addition, food preparation and processing can destroy up to 100% of naturally occurring folate, as it is sensitive to light and air but especially heat. As such, both supplementation and fortification of foods is likely to be a more reliable means of increasing body tissue levels and human folate status than dietary forms.

What does folic acid do?

Folic acid is an essential vitamin, whose main function is as a coenzyme in single-carbon transfers in the metabolism of nucleic and amino acids. It also plays an essential part in the production of purines and pyrimidines that make up DNA, making it a critical nutrient in relation to cell division and repair of genetic material. It also primes the homocysteine molecule for methylation and together with vitamin B12 and vitamin B6; folate effectively lowers homocysteine in the blood through regeneration of methionine. Moreover, the methyl group donated in this process is taken up by the substance, S-adenosyl methionine (S-AdoMet), which in turn participates in various transmethylation reactions throughout the body, including the synthesis of adrenaline, creatine and melatonin.

What are the benefits of folic acid?

- Folic acid reduces the risk of neural tube defects (eg, spina bifida, anencephole) in babies. Women who could become pregnant and for the first 12 weeks of pregnancy are recommended to take 400 micrograms/day of folic acid (5mg/day in case of previous NTDs or where risk is considered to be high, eg, in women taking anti-epileptic medication)
- Evidence from observational studies suggests a protective effect of increasing folate intake on CVD risk. However, randomised controlled trials have not demonstrated a beneficial effect of folic acid on CVD risk ***in people who have established cardiovascular disease.***
- Evidence from prospective studies in humans suggests a trend towards a protective effect of folate intake on colon cancer risk. Some animal studies suggest that folic acid may inhibit tumour development in normal tissues, but promote the progression of established cancer. No RCTs designed to investigate the relationship between folic acid and cancer incidence have yet been published or reported.
- Evidence from observational studies suggests that cognitive impairment and Alzheimer's disease is associated with poor folate status, but evidence from

RCTs, meta-analyses and systematic reviews is inconclusive. However, a recent double-blind RCT in 818 men and women aged 50–70 years found that folic acid 800 µg daily for 3 years significantly improved domains of cognitive function including memory, information processing speed and sensorimotor speed compared with placebo. As part of the same trial, folic acid was also found to slow age-related decline in hearing.

- Evidence exists of a link between depression and low folate status. Evidence from RCTs to date is minimal but positive.

How much do we need?

Table 1: Dietary Reference Values and Upper Levels for folic acid (mcg/d)

EU RDA = 200mcg						
Age	UK RNI	UK EVM	USA RDA	USA TUL	FAO/ WHO RNI	EU SCF
0-3 months	50		65	-	80	
4-6 months	50		65	-	80	
7-12 months	50		80	-	80	
1-3 years		70		150	300	150
4-6 years		100		-	-	200
4-8 years		-		200	400	-
7-10 years	150		-	-	300 ^a	
9-13 years	-		300	600	400	
14-18 years	-		400	800	400	
Males						
11-14 years	200		-	-	-	
15-50+ years	200	1000	400	1000	400	1000
Females						
11-14 years	200		-	-	-	
15-50+ years	200	1000	400	1000	400	1000
Pregnancy	+100 ¹		600	1000 ²	600	
Lactation	+60		500	1000 ²	600	

a = 7-9 years

1. The Department of Health recommends that all women who are pregnant or planning a pregnancy should take a folic acid supplement (see dose)

2. ≤ 18 years = 800mcg daily

EVM = FSA Expert Vitamin and Mineral Group Guidance on Likely safe daily intake from supplements alone

USA TUL = Tolerable Upper Intake Level (defined by the Food and Nutrition Board of the US National Academy of Sciences as the highest total level that could be consumed safely on a long-term daily basis and unlikely to cause adverse health effects in the general population)

EU SCF = Tolerable Upper Intake Level defined by the EC Scientific Committee on Food as the maximum level of chronic daily intake unlikely to pose a risk of adverse effects to humans.

Notes on Dietary Reference Values:

- The current UK RNI is 200 micrograms daily for food folates. *This figure takes into account the poor bioavailability of food folate. It is difficult to make a case to say that the RNI for folate may not be met because of this poor bioavailability, since poor bioavailability is accounted for in the estimation of the RNI.*
- The EU RDA used as a reference for food supplement labelling purposes is 200 micrograms daily
- National reference values in other countries vary from 200-400 micrograms daily
- The US RDA for adult men and women is *400 micrograms daily*
- The FAO/WHO population reference intake for adult men and women is *400 micrograms daily*
- The SCF has published an opinion on the revision of reference values for food labelling of *400 micrograms folate per day*

Safe Upper Levels

- The EU Scientific Committee on Food (SCF) has proposed an upper level of 1000 micrograms for chronic or long-term daily intake for folic acid. This is based on a Lowest Observed Adverse Effect level (LOAEL) of 5000 mcg and an Uncertainty Factor (UF) of 5 and also on a No Observed Adverse Effect level (NOAEL) of 1000 mcg and an UF of 1.
- The US Food and Nutrition Board (FNB) established a UL of 1000 mcg/day for chronic intake of folic acid.
- The UK EVM did not set a SUL for folic acid as available evidence on adverse effects was not considered to be sufficiently robust. A Guidance Level of 1000 mcg/day was set for folic acid based on concerns that intakes above this could mask signs of B12 deficiency.
- The Scientific Advisory Committee (SACN) on Nutrition's Report on folic acid confirmed that there are no data to suggest that vitamin B12 deficiency diagnosis will be delayed at an intake of folic acid below 1000 mcg daily
- SACN stated that there is no increased risk of cancer at levels of folic acid < 1000 mcg daily
- All ULs set to date refer to folic acid not folates.
- All risk assessments conclude that there is no known risk from food folate intake
- No scientific body has set a UL for food folates

UK folate intakes

Table 2: Folate acid intakes from the National Diet and Nutrition Survey (NDNS) in adults aged 19-64 years

	19-64 years	19-24 years	25-34 years	35-49 years	50-64 years
Mean daily intake (men) (mcg)	344 (177% RNI)	301 (151% RNI)	346 (173% RNI)	343 (171% RNI)	361 (181% RNI)
Mean daily intake (women) (mcg)	251 (125% RNI)	229 (114% RNI)	233 (117% RNI)	255 (128% RNI)	268 (134% RNI)
% men below RNI*	11 (11)	14 (14)	9 (8)	10 (10)	10 (10)
% women below RNI*	30 (28)	40 (35)	36 (35)	28 (26)	25 (22)
% men below LRNI*	0(0)	2(2)	0(0)	0(0)	0(0)
% women below LRNI*	2(2)	3(3)	2(2)	2(1)	2(2)
Mean intakes in upper 2.5 per centile (men)*	612 (680)	535 (565)	617 (680)	605 (633)	637 (754)
Mean intakes in upper 2.5 per centile (women)*	451 (554)	444 (557)	403 (573)	463 (551)	465 (572)

* Brackets - from all sources including dietary supplements
RNI = 200 mcg/day for adult men and women

Notes

- 13 million people (25% of the UK population) have folic acid intakes below the RNI of 200 micrograms daily
- 34% of adult women of childbearing age have intakes below the RNI
- 37% of people over the age of 65 years have intakes below the RNI
- 86% of women aged 19-24 years, 92% of women aged 25-34 years and 85% of women aged 35-49 years have intakes of folic acid from all sources (including supplements) below 400 micrograms daily
- In the recent FSA low income survey, mean intake of folic acid was 214 mcg/daily; 7% of women in this group had intakes of less than 100 mcg/day; mean intakes in the upper 2.5 per centile intake was just over 400 mcg/day
- 127,000 people currently have very high folic acid intakes (exceeding 1000mcg daily).

Folate status: red cell folate and serum folate

Red cell folate is considered to be a better measure of long term folate status than plasma folate because it reflects body stores at the time red blood cells are made.

Table 3: Folate status from the National Diet and Nutrition Survey (NDNS) in adults aged 19-64 years

	19-64 years	19-24 years	25-34 years	35-49 years	50-64 years
Mean red cell folate (men) (nmol/l)	694	561	688	677	773
Mean red cell folate (women) (nmol/l)	685	576	630	691	768
% men red cell folate severely deficient	1	-	1	1	-
% men red cell folate marginal	4	13	3	4	2
Mean red cell folate lower 2.5 percentile (men)	287	231	319	278	360
% women red cell folate severely deficient	0	-	-	-	0
% women red cell folate marginal	5	8	4	5	6
Mean red cell folate lower 2.5 percentile (women)	685	576	630	691	768
Mean serum folate (men) (nmol/l)	20.8	17.4	20.1	20.9	22.9
Mean serum folate (women) (nmol/l)	22.1	20.6	21.2	21.9	23.7
% men serum folate deficient	1	-	1	1	1

Mean serum folate lower 2.5 percentile (men)	8.1	7.2	8.8	9.4	7.8
%women serum folate deficient	0	-	-	0	-
Mean serum folate lower 2.5 percentile (women)	8.9	9.2	8.4	8.6	9.3

Notes

- In adults, a *red cell* folate concentration below 230nmol/litre is considered to be severely deficient
- *Red cell* folate concentrations between 230 nmol/litre and 345 nmol/litre indicate marginal status. Concentrations of 422-1463 nmol/litre are considered normal
- Normal range for *serum* folate concentration in adults is considered to be between 7nmol/litre and 46 nmol/litre with concentrations less than 6.3nmol/litre being considered deficient.
- 4% of men and 5% of women had a concentration of red cell folate indicating marginal status
- No more than 1% of any sex/age group had a red cell folate indicative of severe red cell folate deficiency
- 1% of men and less than 0.5% of women had a serum folate concentration below the lower level of the normal range
- 8% of women aged 19-24 years, 4% of women aged 25-34 years and 5% of women aged 35-49 years had a concentration of red cell folate indicating marginal status.
- 13% of men aged 19-24 years had a red cell folate concentration indicating marginal status.

Arguments against FSA proposal to set cap on contributions for folic acid supplementation at 200 mcg/day

- EU RDAs are being revised and could be set at 400 microgram; the SCF has published an opinion on the revision of reference values for food labelling of *400 micrograms folate per day*. If the RDA is changed, food supplements could require reformulation and relabelling.
- The UK RNI of 200 micrograms was set in 1991 – before the DH recommendations for women of childbearing age and pregnancy.
- The SACN report on folic acid and folic acid fortification of food recommended fortification, and also recommended that advice be given on appropriate supplement use. SACN did not recommend changing the formulation of supplements.

- The SCF and USA Food and Nutrition Board have set Upper Levels of 1000mcg daily for chronic/long term intake of folic acid from supplementary folic acid. This does not include naturally present food folates.
- The UK EVM did not set a UL for folic acid due to the absence of robust data. Instead, the EVM set a guidance upper intake level of 1000mcg folic acid daily from food supplements based on concerns that intakes above this level could mask B12 deficiency. This figure does not include food folates.
- SACN confirmed there is no increased risk of cancer at levels of folic acid below 1000mcg daily
- SACN confirmed there are no data indicating masking of vitamin B12 deficiency with folic acid intakes up to 1000mcg.
- All upper levels relate to folic acid; all risk assessments conclude there is no risk from food folates. No national body has set a UL for food folates.
- Maximum permitted levels (MPLs) for food supplements are still to be established. Proposals for MPLs made so far are as follows:
 - The European Responsible Nutrition Alliance (ERNA) and the European Federation of Associations of Health Product Manufacturers (EHPM): 600 micrograms.
 - The German Federal Institute for Risk Assessment Institute: 400 micrograms.
 - David Richardson (In Food Science and Technology Bulletin, 2007: Functional Foods 4(6) 51-66): 600micrograms.
 - Current food supplement industry guidelines established in 1997: 400 micrograms.
- Many multivitamins provide 200mcg but if MPLs set at 400mcg, there is a need for flexibility in formulation
- A cap of 200micrograms daily for folic acid in food supplements for the general population would create confusion for women of childbearing age who require 400 micrograms daily. This confusion would occur despite the FSA not planning to cap supplements for this group of women. Special recommendations and labelling of supplements would be required.
- 86% of women aged 19-24 years, 92% of women aged 25-34 years and 85% of women aged 35-49 years have intakes of folic acid from all sources (including supplements) below 400 micrograms daily. Increasing confusion about folic acid supplementation for women of childbearing age (including those below 19 years) could create a serious public health problem.