ABSTRACT

The Norwegian Scientific Committee for Food Safety (VKM) received a request from the Norwegian Food Safety Authority to assess whether the Tolerable Upper Intake Level (UL) of folic acid should be amended in light of new scientific evidence suggesting a possible link between high intake levels of folic acid and risk of cancer. Folic acid obtained from both food supplements and fortified foods should be assessed. Folic acid is a synthetic form of folate and is commonly used in food supplements and in food fortification because of its stability and bioavailability. Folic acid is reduced, methylated and released into the circulation. Natural folates occur in reduced forms, e.g. as tetrahydrofolate (THF), which are unstable and may thus loose biochemical activity during harvesting, storage, processing, and preparation.

Folate is cofactor for enzymes in one-carbon metabolism where it provides one-carbon units for the formation of RNA and DNA. Folate is also essential for the normal functioning of the methionine cycle, which is responsible for both the conversion of homocysteine to methionine and the production of the universal methyl donor S-adenosylmethionine (SAM). SAM donates its methyl group to more than 100 methyltransferases for a wide range of substrates such as DNA, hormones, proteins, neurotransmitters and membrane phospholipids.

While no Tolerable Upper Intake Level (UL) has been derived for natural dietary folates, the Scientific Committee on Food (SCF, 2000) set an UL of 1000 µg folic acid per day in 2000. The UL was set because it was found that high intakes of folic acid could correct megaloblastic anemia, which is the hallmark manifestation of vitamin B_{12} deficiency. In this way folic acid may mask vitamin B_{12} deficiency which again may cause irreversible neurological damage. The ULs for...
children and adolescents (1-17 years) were adjusted on the basis of body weight and range from 200 to 800 µg/day. The UL for folic acid has been reassessed by other authorities, most recently in 2009 by EFSA (EFSA, 2009), who upheld an UL of 1000 µg/day.

In 2009, Ebbing et al. published results from combined analyses of two randomised, placebo-controlled trials with B-vitamin supplementation in patients with ischemic heart disease. They found an increased risk of cancer in those who were randomised to receive folic acid in combination with vitamin B₁₂ (Ebbing et al. 2009). Folates are important for cell division. It is therefore possible that tumor growth or growth of premalignant cells may be stimulated by high concentrations of folate in the blood. Another concern with use of folic acid is circulating unmetabolised folic acid (UMFA) which is often found at intakes of more than 200 µg per day (Kelly et al. 1997). It has been argued that UMFA could affect homeostatic regulation of folate (Smith et al. 2008), and that it may reduce natural-killer cell cytotoxicity (Troen et al. 2006). In vitro studies have also demonstrated that folic acid can down-regulate tumor suppressor genes (Lubecka-Pietruszewskas et al. 2013).

This opinion addresses the question whether the current UL for folic acid should be amended based on new scientific evidence. Furthermore, VKM has been requested to estimate folic acid intake from food supplements and from foods that are fortified with folic acid, in all age groups in the population above 1 year. In addition, possible consequences of amending the maximum limit for folic acid in food supplements should be discussed.

In the literature search for this opinion (articles published from 2009 to 15 October 2014 were obtained), we found eight meta-analyses and five single studies where the aims were to study the relation between folic acid supplementation and incidence of cancer. Meta-analyses including studies in which folic acid was used in combination with other supplements were not included in the final evaluation, as the effect of folic acid could not be distinguished from the effect of the other substances. Only one meta-analysis was therefore considered relevant for the evaluation of UL for folic acid; a meta-analysis of patients with colorectal adenomas who received 1 mg folic acid per day for 3-6 years (Figueiredo et al. 2011). No increased risk of colorectal adenomas or cancer was found in this meta-analysis. Nor did the included single studies report increased risk of colorectal cancer following folic acid supplementation (Gao et al. 2013; Wu et al. 2009).

Brain tumor and childhood leukemia were investigated in two case-control studies in offspring of women using folic acid supplementation during pregnancy (Amigou et al. 2012; Milne et al. 2012). Both studies indicated no negative effects of folic acid supplementation during pregnancy.

A secondary analysis of one of the single studies on colorectal adenomas found a statistically significant increased risk of prostate cancer following folic acid supplementation (Figueiredo et al. 2009). However, the small number of prostate cancer cases in this single study does not make this result robust.

In six studies circulating UMFA was reported among subjects who used folic acid supplements or who were subjected to folic acid food fortification. Whether UMFA contributes to the development of cancer or other undesirable health effects is not known. These studies do not provide new evidence for amending the existing UL for folic acid.

About 26% of women and 18% of men aged 18-70 years participating in the nationwide dietary survey Norkost 3, reported to take folic acid supplements. The mean intake of folic acid among users was 149 µg/day among women and 172 µg/day among men. Among pregnant women participating in The Norwegian Mother and Child Cohort Study, 62% reported use of folic acid supplements in 2008. Mean folic acid intake was 388 µg/day, and the 95th percentile was 800 µg/day. Information on intake of folic acid from supplements for other age groups is not available.

Intake of folic acid from fortified foods is not available in the national food consumption surveys for any age groups. However, according to a Norwegian model for food fortification from 2006 and later updates (last update in 2013), 53 µg folic acid per 100 kcal can be added to food and drinks.
without exceeding the UL for folic acid in any age groups. With the current levels of folic acid in food supplements and current levels in fortified products, the UL for folic acid will not be exceeded.

VKM was also requested to assess the impact of any increase of the current maximum limit of 200 µg for folic acid in supplements. Increasing the maximum limits in food supplements to 400 µg will imply exceedance of UL for children younger than 6 years and an intake close to UL in children 7-10 years. An increase in the maximum limits in food supplements to 600 µg will imply exceedance of UL for children younger than 10 years and an intake close to UL in children 11-14 years. Increasing the maximum limits in food supplements to 400 µg or 600 µg will not imply exceedance of UL among adults as evaluated in the Norwegian food fortification model (VKM, 2013).

No new evidence for increased risk of cancer related to folic acid was found in the reviewed literature. Studies in subjects who had a history of colorectal adenomas, a group considered particularly vulnerable to develop cancer, reported no increased risk of colon cancer or adenomas after 3-5 years of treatment with 1000 µg of folic acid per day. VKM therefore concludes that studies published after 2009 and until 15 October 2014 examining cancer do not provide support to alter the existing UL for folic acid.

Keywords: Folic acid; tolerable upper intake level; UL; risk assessment; VKM; Norwegian Scientific Committee for Food Safety.

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NOTE:

The authors have prepared the draft opinion. The opinion has been assessed and approved by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of VKM.

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