

FOLIC ACID: A TOXICOLOGIST' VIEWPOINT

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<http://www.iss.it/inte/>

ARE THERE ADVERSE EFFECTS OF CONCERN?

Question marks for discussion

Hazard identification (What adverse effects ?)

“Toxicity” ?

Interference with other dietary components ?

Interactions with toxic compounds ?

Dose-response ?

Vulnerable groups ?

**e.g., people with metabolic problems, ongoing
diseases...**

CURRENT EU ASSESSMENT

Scientific Committee on Food, 2000:

Upper Level of intake (UL)

**of folic acid (FA) = 1 mg/die in the adult
(proportionally related to body weight
in **adolescent/child**)**

Based on

**Masking of the onset on neurological
effects associated with vitamin B12
deficiency**

CURRENT EU ASSESSMENT

(2)

Two considerations made by SCF:

The UL is conservatively based on a
(*allegedly ?*) small *vulnerable subgroup with*
enhanced nutritional/metabolic vulnerability

Changing dietary patterns may influence the
frequency of vulnerable subjects:

***vegetarians/vegans* may be more at risk of**
vitamin B12 deficiency

**WHAT NEW RELEVANT
INFORMATION
SINCE THEN ?**

Hazard identification (1)

“Toxicity” ?

**No significant evidence for “direct”
toxicity at excessive intake level.**

**FA is not like other micronutrients, e.g.,
some trace elements**

Interference with other diet components

No new relevant data on the *alleged* interference with Zinc (SCF, 2000)

High levels of **polyphenols** (e.g., quercetin) may increase homocysteine production, thus **enhancing** FA requirements (Hultberg et al., *Clin Biochem*, 2006)

However, dietary patterns in EU are evolving.

*It might be interesting to investigate **specific situations** such as intake of nutraceuticals, veganism etc.*

Interactions with toxic compounds ?

Indeed,

- **alcohol consumption, smoking, some drugs** (trimethoprim, methotrexate, anti-epileptics, contraceptive pills..) may **enhance FA requirements**
- **FA reduces NTDs and oxidative stress induced by arsenic** in rodents (*Reff. in database EDID-Endocrine Disruptors Diet Interactions in <http://www.iss.it/inte/>*)

Interactions with toxic compounds ?

**Therefore, there is no evidence of FA
potentiating effects of xenobiotics**

**whereas, some situations related to lifestyles,
pharmaceutical treatments, environmental
pollution**

**(arsenic in Bangladesh: Gamble et al., *Env
Health Perspect* 2005 and *Am J Clin Nutr*,
2006)**

may increase FA requirements

Specific effects in population groups

1) FA AND TWINNING

2) FA AND CANCER

FA AND TWINNING

Increased rates of twinning AND increased periconceptional FA appear to parallel

A link ?

Hungary : doubling the rate of dizygotic twin pregnancies with FA periconceptional supplementation (Czeizel and Vargha, *Am J Obstet Gynecol.* 2004)

**USA (metropolitan Atlanta vital records):
Increasing twinning trends only in women > 30 years; trends began prior to folic acid fortification (1996) and reached a plateau (Kucik and Correa, *J Reprod Med.* 2004)**

Increase of IVF pregnancies is a strong confounder:
strongly associated **both** with twin pregnancies **and**
folate use as shown in **Norway** (Vollset et al.,
Epidemiology, 2005)

However

Sweden: doubling the rate of dizygotic twin pregnancies
with FA periconceptional supplementation in women
non-immigrated **and** not undergoing fertility
treatments (Kallen, *Early Hum Dev.* 2004) (*possible
confounder maternal age*)

USA: twin gestation rates in women not using fertility
treatments (**nulliparous, 16-19 yrs**) increased after
start of food fortification with FA resulting in a
modest but steady increase of 2 additional twin
pregnancies per 10,000 births per year in 1996-2000
(Signore et al., *Obstet Gynecol.* 2005)

Thus, conflicting evidence

Genetic background ? Confounding factors ?

The toxicologist feels uneasy

- Dose response ?

- Experimental models to support any biological plausibility ?

(see review by Levy and Blickstein *Int J Fertil Womens Med.* 2006)

Should we look more closely to specific subgroups ?

There are hints about

Folate supplementation required by subjects with sickle cell disease may increase twinning (*high dosages* ?)

(Ballas et al., *Am. J. Hematol*, 2006)

In women having a successful IVF pregnancy, high folate status (plasma/RBC) increases (up to + 50%) the likelihood of twin birth after multiple embryo transfer (Haggarty et al., *Lancet*, 2006)

IVF not just a confounder ?

FA AND CANCER

Although not uniformly consistent, epidemiologic studies generally suggest an inverse association between dietary intake and/or blood measurements of folate and risk for several cancer (breast, ovary, pancreas..).

Positive effects appear more evident in subjects with low folate intake (e.g., Martinez et al., *Int J Cancer*, 2006), alcohol consumption (Larsson et al., *J Natl Cancer Inst*, 2007) or smokers.

BUT a few recent studies indicate that for some cancers things might not be so straightforward

PROSTATE CANCER

(Sweden) Increasing plasma levels of folate associated with prostate cancer risk (OR 1.60, 95% CI = 1.03-2.49); after adjustment for body mass index and smoking, OR was 1.30 (95% CI = 0.74-2.24) (Hultdin et al., *Int J Cancer* 2005)

In this group 677 CT genotype had increased risk (OR 1.52, 95% CI 1.02-2.26) but not the TT (OR 0.91 (Van Guelpen et al., *Eur J Cancer Prev.* 2006)

Both Hultdin et al. and Weinstein et al (Am J Nutr 2006) showed that vitamin B-12 intake significantly increased the risk

BREAST CANCER

(Canada, USA) Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial

The risk of developing breast cancer was significantly increased by 20% in women reporting supplemental folic acid intake during pregnancy > or = 400 mcg/d compared with those reporting no supplemental intake.

Food folate intake was not significantly related to breast cancer risk,

Total folate intake, mainly from folic acid supplementation, significantly increased breast cancer risk by 32%

(Kim, *Nutr Rev* 2006; Stolzenberg-Solomon RZ, *Am J Clin Nutr*, 2006)

COLON CANCER

(NL): Relatively high folate dietary intake **reduced** the risk of APC(-) colon tumors, **but** folate intake was **positively associated** with APC(+) colon tumors among males, not women (highest vs. lowest tertile: RR 2.77, 95% CI 1.29-5.95,). (DeVogel et al., *J Nutr* 2006)

(Sweden) A clear dose-related association **only** in subjects with the longer follow up time (greater than 4.2 years).

In these fraction of subjects plasma folate was strongly positively related to colorectal risk; (highest versus lowest quintile RR 3.87, 95% CI 1.52-9.87).

No association with homocysteine (Van Guelpen, *Gut*, 2006)

Possible mechanisms ?

Embryonic and cancer tissues **are similar** concerning one-carbon metabolism in **mitochondria**, primarily supporting cytosolic purine and pyrimidine synthesis (Nijhout HF, *Theor Biol Med Model.* 2006)

Folate receptor alpha binds and transports folate into cells. FRalpha levels are **high in specific malignant tumors of epithelial origin** compared to normal cells, and are positively associated with tumor stage and grade, possibly conferring a growth advantage (Kelemen *Int J Cancer* 2006)

Folate deficiency induces a pronounced global increase in **miRNA expression** (*What about high folate ?*)

(Marsit et al., *Cancer Res.* 2006)

Tissue specific effects ?

Colon cancer: C677T is associated with increased homocysteine levels and DNA hypomethylation **BUT** most studies have reported a reduced risk associated with this polymorphism (Van Guelpen, *Gut*, 2006). **Localized folate depletion might impacts on the DNA synthesis pathway** (Brockton *Cancer Causes Control*. 2006)

The **prostate**-specific membrane antigen (PSMA), a product of the folate hydrolase gene, is highly expressed in malignant prostate tissues. **High folate favours PSMA expression** which in turns gives a growth advantage to prostate cancer cells (Yao and Bacich, *Prostate*, 2006)

Other issues for caution?

Studies in rats have demonstrated that mild folate deficiency **reduces the incidence and size** of chemically-induced (N-methyl-N-nitrosourea) mammary tumors

No effects of folate high doses (8 mg/kg bw)

(Kotsopoulos et al., *Carcinogenesis*, 2005)

Low FA may reduce **malignant progression of benign lesions ?**

- Is there a potential for interference **with treatments** for important, public health problems

Cancer

but also **Rheumatoid arthritis** (methotrexate) ?

Again, the toxicologist feels somewhat uneasy

- **In particular because of weak dose - response data (is there a “threshold” for non-beneficial effects of FA) ?**
- **How much and what other factors, genetic and non-genetic, do matter ?**

Any Conclusion ?

Available data

- **cannot throw any doubt** on consolidated policies to maximise FA benefits (promotion of healthy diets, periconceptional supplementation, targeted campaigns in vulnerable populations, etc.)
- do provide **sufficient ground to warrant further research** on some potential adverse effects of high folate intake, in particular **cancer**
- Other factors related to lifecycle, genotype as well as diet/lifestyle have be considered (**either as confounders or as cofactors**) to assess any potential risk from high folate intake

Any Conclusion ?

Dioxin: the least in our food, the best
FA may not be the most the best

Caution should be adopted towards policies aimed to increase the folate intake above established requirements in the general population, with its widespread range of age groups, genotypes, lifestyles, disease predispositions

A topic important for EFSA

**EFSA Colloquium 6: Risk-benefit
analysis of foods: methods and
approaches - 13 -14 July 2006**

(priority issues included

**“Risk and benefit analysis of food
fortification and “functional foods”)**

http://www.efsa.europa.eu/en/science/colloquium_series/risk_benefit_analys.html