

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Folic acid – Further papers

1. The COC considered the issue of at its July 2006 meeting. The committee recommended a precautionary approach in considering mandatory fortification of flour with folic acid. The Chairman subsequently agreed, in discussion with the FSA, that this recommendation was consistent with that of the Scientific Advisory Committee on Nutrition (SACN) for the mandatory fortification of wheat flour, with controls on voluntary fortification and advice on the use of supplements. This is now reflected in the revised SACN paper to the FSA Board “Options for improving folate intakes of women of reproductive age and preventing neural tube defects” (see <http://www.food.gov.uk/multimedia/pdfs/fsa070504rev.pdf>). SACN’s recommendation for mandatory fortification includes the proviso that the folic acid intakes and status of the UK population and postulated risks, including cancer, are carefully monitored and that the data on the benefits and possible risks are reviewed five years after the introduction of mandatory fortification.

2. At the last meeting, Members saw an abstract of a paper on a randomized clinical trial of folic acid supplementation for preventing colorectal adenomas which reported no reduction in risk. The full paper by Cole et al (2007) is now published and is attached at Annex B. Also attached are two recent commentaries from the BMJ and a paper by Murtaugh et al (2007) which reports the results of a US case-control study on folate and co-factors in folate metabolism, MTHFR polymorphisms, and risk of rectal cancer.

3. Members are asked if they have any further comments on the issue of folic acid fortification and carcinogenesis?

Secretariat
June 2007

Extract from minutes of the COC meeting on 13 July 2006

ITEM 4: Folic acid fortification and carcinogenesis (CC/06/14) [closed session]

16. The minutes of this item will be published when the report of the Scientific Advisory Committee on Nutrition (SACN) on “Folate and disease prevention” is published.

17. Dr Carthew declared a personal, non-specific interest.

18. Folate is the generic term for a naturally occurring family of B-group vitamins comprising an aromatic pteridine ring linked to *p*-aminobenzoic acid and a glutamate residue. Folic acid (pteroylmonoglutamic acid) is the synthetic form commonly used in supplements and food fortification.

19. In 2000, the Committee on the Medical Aspects on Food and Nutrition Policy (COMA) concluded that the universal fortification of flour with folic acid would significantly reduce the number of conceptions and births affected by neural tube defects (NTDs).

20. In September 2003, the Scientific Advisory Committee on Nutrition (SACN) was asked to assess the evidence that had arisen since publication of the COMA report on folic acid. The SACN draft report on ‘Folate and Disease Prevention’ was published in November 2005. In its draft conclusions, SACN recommended mandatory fortification of flour to reduce NTD risk. SACN subsequently requested further time to reconsider its advice following some concerns about high intakes of folic acid and cancer risk.

21. SACN considered a wide range of evidence on folic acid and cancer risk and noted that most epidemiological studies have shown a protective effect of folate against tumours. However, it noted that, in some animal studies, folic acid consumption is associated with an increase in the incidence of tumours depending on the timing of the intervention. One controlled study in humans (abstract only), which has not yet been published in the peer reviewed literature, shows a significant increase in colorectal adenoma multiplicity following supplementation with folic acid (1mg/d).

22. SACN has asked the COC to review the data on folic acid and cancer risk and to give its opinion on whether dietary folic acid intake is associated with increased cancer risk. The data provided in CC/06/14 include animal studies, a review of epidemiological studies of folate intake and colorectal neoplastic risk, preliminary information from one recent unpublished controlled trial, and the abstract of another controlled trial. A paper on folic acid and breast cancer risk (Charles *et al*, 2004), two papers reporting trials which had examined folic acid supplementation on cardiovascular disease (CVD) outcomes but had also reported effects on cancer risk (HOPE 2 investigators, 2006; Bonna *et al*, 2006) and an

editorial commenting on the CVD prevention trials (Loscalzo, 2006), and a commentary on folate supplementation (Ulrich and Potter, 2006) were tabled.

23. Members were informed that the Recommended Nutrient Intake (RNI) for folate is 0.2 mg/day and that women who are planning a pregnancy are recommended to take an additional 0.4 mg/day until the 12th week of pregnancy. An additional dose of 5 mg/day is recommended for women at high risk of an NTD-affected pregnancy.

24. It was noted that in the US, where mandatory folic acid fortification was introduced in 1998, voluntary fortification of other foods continued to be permitted and blood analyte data indicated that current intakes of folic acid were higher than planned. FSA informed Members that mandatory fortification of flour with folic acid would be subject to tight controls.

25. In response to a query about whether data from the European Prospective Investigation of Cancer (EPIC) on cancer risk and folic acid consumption might be available in the near future, Members were informed by the SACN secretariat that this had not been indicated to them.

26. Members discussed the animal studies summarised in CC/06/14 and noted that the limitations of the experimental approaches had been identified in the papers. Members noted that the animal data suggested that timing of the folic acid administration could be an important factor in potential cancer risk since the data showed that high doses of folic acid may progress the development of pre-existing neoplasms. They commented that the data suggested a possible effect on inherited accelerated colorectal tumourigenesis in mice but not on sporadic colorectal tumourigenesis. It was noted that the dose levels used in several of the studies (e.g. Wargovitch *et al*, 1996; Reddy *et al*, 1996; Le Leu *et al*, 2000) were considerably higher than would be achieved in humans following fortification. A clear dose-response relationship was not apparent in the animal studies as one study (Wargovich *et al*, 1996) showed an increase in the development of aberrant crypt foci at the lower dose of folic acid but not at the higher dose. In addition, the body weight changes in some folic acid deficient groups (16-19% reduction) were a potential confounding factor for rodent tumourigenesis. Overall, the Committee agreed there were multiple plausible mechanisms, including epigenetic mechanisms, whereby folic acid may influence cancer risk. A Member commented that the animal data were equivocal and cautioned against over-interpretation of data from these studies.

27. With regard to the human studies, the Committee considered that these were well summarised in paragraph 12 of CC/06/14. Most epidemiological studies indicate a reduced risk of cancer with increased folic acid or folate intake. It was noted that, in many of the studies, the folic acid had been taken in multivitamins, and the presence of other micronutrients in the multivitamins was a complicating factor. However, Members agreed that preliminary results from one unpublished, randomised trial showed a significant increase in adenoma multiplicity in subjects with a recent history of colorectal adenomas who had been supplemented with folic acid (1 mg/day) for over 3 years. They also noted the results of the two studies of folic acid supplementation on CVD outcomes which showed non-significant

associations between folic acid (in combination with either vitamin B12 or B12 and B6) and cancer. The Committee noted that the reported association by Charles et al (2004) between folate intake during pregnancy and breast cancer mortality was also not statistically significant and was based on small numbers.

28. The Committee noted that there may be susceptible subgroups in the population. It was not possible at this stage to identify these. Factors which might be relevant were age and the presence of pre-neoplastic conditions.

29. It was reported that the COM review of background variation in micronuclei in peripheral blood lymphocytes had indicated that there was good evidence from cross sectional and intervention studies to suggest that plasma or serum folate levels were negatively correlated with micronucleus formation (COM, 2006). In response, it was noted that whether or not risk is increased or reduced may depend on a balance between the thresholds for epigenetic promotional effects and reduction of DNA damage.

30. Members agreed with the comments made by Ulrich and Potter (2006) i.e. that it remains unclear whether the possible deleterious effects of high folic acid outweigh the known and potential health benefits and that this balance may differ across individuals and populations by genetic characteristics and by life stage.

31. In conclusion, a precautionary approach was recommended in considering mandatory fortification of flour with folic acid.

Annex B to CC/07/13

Cole BF et al (2007). Folic acid for the prevention of colorectal adenomas. JAMA 297: 2351-2359.

Wald NJ and Oakley GP (2007). Should folic acid fortification be mandatory? BMJ 334: 1252.

Hubner R, Houlston RD and Muir KR (2007). Commentary from BMJ 334: 1253.

Murtaugh MA et al (2007). Dietary intake of folate and co-factors in folate metabolism MTHFR polymorphisms, and reduced rectal cancers. Cancer Causes Control 18: 153-163.

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