

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

COT position paper on the current upper level for folic acid intake

It is well established that supplementation with folic acid can reduce the risk of having a neural tube defect (NTD) affected pregnancy. UK Government advice is that women should take a folic acid supplement prior to conception and up to the third month of pregnancy. However, as many women do not take supplements and many pregnancies are unplanned, the rate of NTD-affected pregnancies has not significantly changed.

Consequently, the Scientific Advisory Committee on Nutrition (SACN) have recommended that wheat flour should be fortified with folic acid to improve the folate status of the population and thereby reduce the risk of having a NTD affected pregnancy. This recommendation came with the proviso that fortification should not increase the total number of people in the population who were currently exceeding the Upper Level (UL/GL) for folic acid intake of 1 mg/day.

Maximum recommended levels of intake have been set by a number of regulatory authorities based on the observation that folic acid may mask or delay the diagnosis of pernicious anaemia, a condition caused by an inability to absorb vitamin B₁₂, by initially improving haematological status while allowing the accompanying neurological damage to progress untreated.

ULs were set by the US Institute of Medicine Food and Nutrition Board (IOM) and the EU Scientific Committee on Food (SCF) while the UK Expert Group on Vitamins and Minerals (EVM) set a GL of 1 mg/day rather than an UL as they considered that the database was insufficient to set a UL. The COT have also used the term GL, to reflect the considerable uncertainties. Both the SCF and IOM also considered that it was not possible to rule out the possibility that folic acid could directly exacerbate the neurotoxicity associated with pernicious anaemia, although both noted that there was no clear evidence for this in humans. All three bodies used largely the same database of case reports, small human volunteer studies and a limited number of animal studies to make their recommendations.

A recent paper by Wald *et al.*, 2018¹ argued that the basis of the UL is flawed. The criticisms made in the paper apply to the IOM UL but some will also be relevant to maximum intakes recommended by EVM and SCF, as some of the same endpoints were used to set the UL. The Committee on Toxicity discussed this analysis in a scoping paper in March 2018. As a result of this, Members agreed that the original

¹ Wald, N.J., Morris, J.K., Blakemore, C. (2018). Public health failure in the prevention of neural tube defects; time to abandon the tolerable upper intake level of folate. *Public Health Reviews*, 39:2.

UL should be reconsidered, firstly by considering the basis on which it was set and then, if required, consideration of the rest of the database to determine whether a UL was necessary based on other endpoints.

At its meeting in July 2018, the Committee considered the original data used to set the ULs and GL. They also reviewed information on the symptoms, diagnosis, prevalence and treatment of pernicious anaemia.

Given the interest in this topic it was agreed that it would be appropriate for the Committee to publish interim conclusions while further analysis of the data was being conducted.

The COT concluded that:

- a) Consumption of folic acid can mask or delay the diagnosis of pernicious anaemia by improving the anaemia, whilst having no effect on the neurological damage resulting from vitamin B₁₂ deficiency, hence allowing this to progress, possibly becoming irreversible.
- b) At present, the diagnosis of pernicious anaemia is difficult and there is a lack of a reliable, routinely-applicable diagnostic test for pernicious anaemia-associated vitamin B₁₂ deficiency, meaning that this endpoint is still relevant for setting the UL/GL.
- c) The data available are not sufficient to allow a clear dose-response relationship to be established for folic acid masking of pernicious anaemia, possibly because duration of consumption may be important as well as dose.
- d) There is no convincing evidence that folic acid directly causes neurotoxicity, either in the presence or absence of pernicious anaemia.
- e) Further work is needed to identify the maximum level of folic acid intake at which masking would not occur. However, it is very unlikely that this would be such that the GL for intake would be less than 1 mg/day, as at present.
- f) The Committee observed that the development and routine availability of a reliable diagnostic test for pernicious anaemia would render masking irrelevant for setting a GL, although it would be necessary to determine whether any other health outcomes were of concern. The Committee noted that any UL/GL based on such an endpoint would be more than 1 mg/day.