

# A Comment on Safe Upper Levels of Folic Acid, B<sub>6</sub> and B<sub>12</sub>

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This brief review concerns the three main players that jointly lower blood homocysteine (Hcy) as seen by the U.K. Expert Group on Vitamins and Minerals (EVM).<sup>1</sup> The Group concerns itself with "Safe Upper Levels" (SULs) and produces an exhaustive review with many references. Their mandate clearly excluded considerations of "optimal" levels that may well be higher than SULs for therapeutic reasons or to obtain optimal (minimal) levels of Hcy, an amino acid and "natural blood toxin" linked to about 100 illnesses. Other players in Hcy metabolism (reduction) include vitamin B<sub>2</sub>, zinc, magnesium, betaine, and fish oil omega-3.

## Folic Acid

In the U.S.A., 30 g tablets of folic acid can be obtained by mail-order; in the U.K., doses over 5 mg require a prescription. Doses of 1-20 mg/day would be considered safe (p. 44) if it were not for a vitamin B<sub>12</sub> deficiency masking problem, and for some anti-folate drugs, such as methotrexate. Recommended daily intakes are 0.2 mg/day in the U.K. and double that in the U.S.A. Actual mean intakes are near those amounts in these countries respectively.

There is no argument by the EVM of proven or potential benefits regarding Hcy, neural tube defects and other therapies. "The main concern" about folic acid is its potential for masking a vitamin B<sub>12</sub> deficiency at over 5 mg/day and thus a "guidance level" of 1 mg/day supplemental was concluded. Later in the report a SUL for B<sub>12</sub> is given of 2 mg/day, a massive amount of about 1,300 times recommended daily intakes. One must wonder why then the EVM did not issue a much higher SUL for folic

acid in B<sub>12</sub> replete individuals, especially in the light of the statement that "no likely mechanisms for toxicity have been hypothesized" for folic acid.

## Pyridoxine - Vitamin B<sub>6</sub> (see also p. 161)

Recommended daily intakes are about 1.3 mg/day. Deficiency is "unusual" in humans and mean intakes are ~2 mg/day. Therapeutic doses, for example, in carpal tunnel syndrome, may be well in excess of 100 mg/day and side effects (neuropathy) are "generally" reversible. Dr. K. S. McCully, discoverer of the deleterious effects of Hcy, expressed concern (private communication) about the low recommended intake level that should be about double, or 3 mg/day, making most people deficient by their actual intakes. Doses of 50-300 mg/day have been taken for as long as 20 years without neurotoxicity and with reduced myocardial infarction and extended life span.<sup>2</sup>

The EVM bases its SUL on a single-dose Lowest Observed Adverse Effect Level (LOAEL), in dogs, of 30 g, and then applies an arbitrary safety factor of 300 to arrive at a SUL of 10 mg/day. This is a low-dose but one that is about 5 times that of common intakes and one that would be expected to help lower Hcy in most individuals. The EVM laments the lack of long-term safety data below 200 mg/day but suggests risk below this level "may well be minimal" on the short-term.

## Cobalamin - Vitamin B<sub>12</sub>

Recommended intakes are about 1.5 mcg/day with liver and meats containing from ~0.5 (chicken), ~3 (beef) and liver ~20+ mcg/100 g (3.5 oz) serving. Deficiencies are more common in vegans and in elderly, the latter primarily due to (common) absorption problems.

The EVM concludes on a SUL of 2 mg/

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day, a level well in excess of any level of common benefit. Supplements may contain amounts such as 0.1 mg which should circumvent absorption problems in nearly everyone, but not necessarily all.

#### Safe Upper Level of Homocysteine

The proposed SULs or guidance levels are, except in the case of B<sub>12</sub>, well above those commonly obtained from foods. Considering the virtually certain and preventable detrimental effects in about 100 illnesses of higher than minimal amounts of Hcy, the question of a SUL for Hcy itself becomes important. This is especially true because of very common genetic disorders that require higher than minimal amounts of nutrients, and the fact that anything one does to a food (refining, canning, freezing, storing) reduces specifically folic acid and B<sub>6</sub> (while B<sub>12</sub> is little affected).

One can argue that a SUL for Hcy in blood plasma is about 8 micromol/L and that supplementation is not necessarily warranted below that level.<sup>3</sup> For people at "mild risk" (in poor diet or age >60 and Hcy 8-12 mmol/L), supplemental amounts of 3 mg/day B<sub>6</sub>, 0.1 mg B<sub>12</sub> and 0.4 mg folic acid are suggested. These amounts increase at "very high risk" (in angina, ischemic attacks, kidney failure, diabetes and Hcy 16-30 mmol/L) to 100 mg B<sub>6</sub>, 1 mg B<sub>12</sub> and 5 mg folic acid.

Based on the EVM report, these amounts are safe with some remaining uncertainty regarding vitamin B<sub>6</sub>. Higher than minimal Hcy (which *de facto* means: low folic acid, B<sub>6</sub> and B<sub>12</sub>) is firmly linked to some of the most devastating illnesses, from heart and vascular diseases, to cancers and Alzheimer's disease. In the next few years important and possibly conclusive randomized controlled trial data should become available. One thing is certain: there is no benefit from higher than minimal blood Hcy levels which, incidentally, is the best marker for sub-optimal nutrition in people and populations.

The Expert Group should revisit their data considering the universal unsafe levels of Hcy in the Western world and elsewhere, and increase the SUL or guidance levels of folic acid and B<sub>6</sub>. If there is merit establishing SULs for the B vitamins, it is at least as important to now do so for homocysteine.

#### References

1. [www.food.gov.uk/multimedia/pdfs/vitamin2003.pdf](http://www.food.gov.uk/multimedia/pdfs/vitamin2003.pdf)
2. Ellis JM, McCully KS: Prevention of myocardial infarction by vitamin B<sub>6</sub>. *Res Commun Mol Pathol Pharmacol*. 1995; 89(2): 208-20.
3. McCully KS, McCully, M: *The Heart Revolution* (chapter 5). HarperCollins 2002.

*Correction:* In *A Comment on Safe Upper Levels of Folic Acid, B<sub>6</sub> and B<sub>12</sub>* in JOM 18.3 & 4, 2003, p. 166-167, the paper's co-author, Kilmer McCully, was omitted. The 30 grams of folic acid in the second paragraph refers to powder, not tablets. The correct unit of measure for homocysteine is micromols per litre.