Vitamin B_{12}

Introduction

Vitamin B_{12} helps maintain the body's nervous system and blood cells and supports the production of DNA. Vitamin B_{12} also helps prevents a type of anemia and has been termed the "anti-pernicious anemia dietary factor." Vitamin B_{12} is also the only known physiologically important compound that contains cobalt, and therefore the various forms of vitamin B_{12} are known collectively as cobalamins.

Vitamin B_{12} is a cofactor in two enzymes that are fundamental in facilitating growth in humans. In the methylcobalamin form, vitamin B_{12} is the direct cofactor for methionine synthetase, the enzyme that recycles homocysteine back to methionine. Here, vitamin B_{12} and folic acid have closely related roles in one-carbon metabolism. In the adenosylcobalamin form, vitamin B_{12} is the cofactor in methylmalonyl-coenzyme A mutase. Both reactions are involved in promoting the rapid growth and proliferation of bone marrow cells and ultimately red blood cells (Expert Group on Vitamins and Minerals [EVM] 2003).

Vitamin B_{12} is essential for the function and maintenance of the central nervous system, and severe deficiency in persons with pernicious anemia produces the neurological disease of posterolateral spinal cord degeneration (Herbert and Das 1994). The direct cause of pernicious anemia, in fact, is vitamin B_{12} deficiency, but the underlying defect is the absence of an intrinsic factor produced by specific stomach cells and needed for intestinal absorption of vitamin B_{12}. Without this intrinsic factor, absorption is greatly reduced or fails, and a severe and persistent deficiency develops that is not preventable by the usual dietary levels of vitamin B_{12}. In addition to the efficient, intrinsic factor-mediated absorption of small quantities of the vitamin from normal dietary intakes of up to about 6 µg, there is also a very low efficiency of absorption of much higher oral intakes (300 to 1,000 µg). Therefore, high daily oral intakes can be sufficient to treat pernicious anemia by utilizing high intake levels coupled with low efficiency absorption resulting in adequate serum levels. However, the usual treatment is a monthly vitamin B_{12}

intramuscular injection, which bypasses intestinal absorption and the requirement for intrinsic factor for absorption (Hathcock and Troendle 1991).

Safety Considerations

No toxic effects of B_{12} have been encountered in humans or animals at any level of oral intake (Miller and Hayes 1982; IOM 1998). The overall evidence indicates that vitamin B_{12} is virtually nontoxic. Doses of 1,000 µg per day were administered to a child by intravenous injection for a year without adverse effect (Merck Service Bulletin 1958). Even if 100 percent metabolic liberation of cobalt from cyanocobalamin is assumed, the cobalt and cyanide contributions of 1,000 µg of vitamin B_{12} are toxicologically insignificant (Hathcock and Troendle 1991). It would be easy to speculate that cobalt is virtually nontoxic because of the low percentage that is absorbed by the intestine from oral intake, but the lack of toxicity of intramuscular injections of vitamin B_{12} argues strongly that the compound is nontoxic even when it is absorbed. This could be due to limited entry of cobalt into cells.

Official Reviews

IOM (1998). The IOM concluded that "no adverse effects have been associated with excess B_{12} intake from food or supplements in healthy individuals." Consequently, this organization concluded that there was no basis for a UL value.

European Commission's Scientific Committee on Food (EC SCF 2000). Likewise, the EC SCF reviewed vitamin B_{12} and found no adverse effects for vitamin B_{12} that could be used to define a LOAEL or NOAEL. They therefore found no basis for deriving a UL value.

EVM (2003). The UK's EVM found no evidence of adverse effects of vitamin B_{12} in humans. They did find that subcutaneous or intraperitoneal injections of 1.5 to 3 mg per kg body weight (100 to 300 mg in average human adults) were acutely toxic to mice (Tsao and Myashita 1993). The report concluded that there was no basis for an SUL for oral vitamin B_{12}, but they did set a

guidance level of 2,000 µg per day based on a clinical trial of Juhlin and Olsson (1997) as well as other data.

European Food Safety Authority (2009). In 2009, EFSA was commissioned by the European Commission to provide a scientific opinion on the safety of vitamin B_{12}-enriched yeast (added for nutritional purposes) and on the bioavailability of vitamin B_{12} from this source. EFSA concluded that it was not possible to assess the bioavailability of vitamin B_{12} from vitamin B_{12}-enriched yeast since neither data nor suitable supporting references were provided. This provided no additional data to support a formal risk assessment of vitamin B_{12}.

CRN Recommendations

Vitamin B_{12} has no observable adverse effects at any level of oral intake, even when consumed parenterally at 1,000 µg (1 mg) twice weekly for up to 3 years or intravenously at 1 mg per day for 1 year. The IOM observation of a lack of any adverse effects for vitamin B_{12}, combined with the extensive testing and use of oral vitamin B_{12} dosages up to 1,000 µg in pernicious anemia patients (Hathcock and Troendle 1991), suggests that high dosages of vitamin B_{12} are safe for such persons.

There was evidence of growth retardation after super-high doses of oral vitamin B_{12} in mice—equivalent to 100 to 300 mg per person per day. At these levels, the adverse effects could be due to dietary dilution of other essential nutrients. Thus, there is no basis for a LOAEL for oral intake.

There is considerable experience and clinical evidence of safety at oral intakes of 3,000 µg (3 mg) per day. Higher intakes may also be safe, and a clinical trial **(**Juhlin and Olsson 1997) confirms this at 2,000 µg per person per day. Thus, the CRN UL for supplemental vitamin B_{12} is set at 3,000 µg per day. Dietary intakes are trivial in comparison with this amount of supplemental intake.

Quantitative Summary for Vitamin B_{12}

CRN UL, supplemental intake	3,000 μg (3 mg)/day
IOM UL, total intake	Not determined
EFSA UL, total intake	Not determined
EC, supplement maximum	Not determined
EVM, guidance level, supplemental intake	2,000 μg (2 mg)/day

References

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