Vitamin B₁₂

Introduction

Vitamin B₁₂ helps maintain the body’s nervous system and blood cells and supports the production of DNA. Vitamin B₁₂ also helps prevent a type of anemia and has been termed the “anti-pernicious anemia dietary factor.” Vitamin B₁₂ is also the only known physiologically important compound that contains cobalt, and therefore the various forms of vitamin B₁₂ are known collectively as cobalamins.

Vitamin B₁₂ is a cofactor in two enzymes that are fundamental in facilitating growth in humans. In the methylcobalamin form, vitamin B₁₂ is the direct cofactor for methionine synthetase, the enzyme that recycles homocysteine back to methionine. Here, vitamin B₁₂ and folic acid have closely related roles in one-carbon metabolism. In the adenosylcobalamin form, vitamin B₁₂ 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 B₁₂ 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 B₁₂ deficiency, but the underlying defect is the absence of an intrinsic factor produced by specific stomach cells and needed for intestinal absorption of vitamin B₁₂. 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 B₁₂. 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 B₁₂
intramuscular injection, which bypasses intestinal absorption and the requirement for intrinsic factor for absorption (Hathcock and Troendle 1991).

**Safety Considerations**

No toxic effects of B₁₂ 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 B₁₂ 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 B₁₂ 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 B₁₂ 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 B₁₂ 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 B₁₂ and found no adverse effects for vitamin B₁₂ 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 B₁₂ 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 B₁₂, 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 B₁₂-enriched yeast (added for nutritional purposes) and on the bioavailability of vitamin B₁₂ from this source. EFSA concluded that it was not possible to assess the bioavailability of vitamin B₁₂ from vitamin B₁₂-enriched yeast since neither data nor suitable supporting references were provided. This provided no additional data to support a formal risk assessment of vitamin B₁₂.

**CRN Recommendations**

Vitamin B₁₂ 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 B₁₂, combined with the extensive testing and use of oral vitamin B₁₂ dosages up to 1,000 μg in pernicious anemia patients (Hathcock and Troendle 1991), suggests that high dosages of vitamin B₁₂ are safe for such persons.

There was evidence of growth retardation after super-high doses of oral vitamin B₁₂ 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 B₁₂ 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\textsubscript{12}

<table>
<thead>
<tr>
<th>Source</th>
<th>Supplemental Intake</th>
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</thead>
<tbody>
<tr>
<td>CRN UL, supplemental intake</td>
<td>3,000 (\mu)g (3 mg)/day</td>
</tr>
<tr>
<td>IOM UL, total intake</td>
<td>Not determined</td>
</tr>
<tr>
<td>EFSA UL, total intake</td>
<td>Not determined</td>
</tr>
<tr>
<td>EC, supplement maximum</td>
<td>Not determined</td>
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<tr>
<td>EVM, guidance level, supplemental intake</td>
<td>2,000 (\mu)g (2 mg)/day</td>
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References


