Vitamin B_{12}

bw	body weight
CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NIH	National Institute of Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Vitamin B12 has been described as the largest and “most complex” vitamin. Vitamin B12 is the only physiologically important compound that contains cobalt, and therefore the various forms of vitamin B12 are known collectively as “cobalamins” (NIH 2025; Drake 2023; Watanabe 2007). Vitamin B12 is not present in plant foods, except for edible algae or blue-green algae; however, it naturally occurs in animal-derived foods (e.g., meat, milk, eggs, fish, and shellfish) and can be synthesized by specific bacteria (Watanabe 2007). Vitamin B12 is critical in the development, myelination, and function of the central nervous system, supports blood cell formation, and assists

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in the production of DNA (Drake 2023; NIH 2025).

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. In the 5'-deoxyadenosylcobalamin form, vitamin B12 is the cofactor in a reaction catalyzed by methylmalonyl-coenzyme A mutase. This reaction converts L-methylmalonyl-CoA to succinyl-CoA, which then enters the citric acid cycle (Drake 2023; NIH 2025). The most common form of vitamin B12 (i.e., cobalamins) used in supplements is cyanocobalamin, which can be converted into these two coenzyme forms following ingestion (Drake 2023; Watanabe 2007).

Bioavailability

Vitamin B12 is released from food in the stomach with help from gastric acid and digestive enzymes. The amount of vitamin B12 absorbed varies depending on the dietary source, the amount ingested, the release of vitamin B12 from food sources, and the proper transport of the vitamin within the body (EFSA 2015).[1] At low doses (up to about 5 µg), the bioavailability of vitamin B12 is 50% when consumed in the diet and 60% when ingested as supplements (Allen 2010). However, an inverse relationship between dose level (via consumption of food or supplements) and rate of absorption has been demonstrated where consumption of higher levels of vitamin B12 (i.e., > 5 µg) result in a lower bioavailability (Allen 2010; Carmel 2020). For example, one study demonstrated that 50% of vitamin B12 was bioavailable when 1 µg was consumed in a meat sample, while less than 10% and 5% were bioavailable from consumption of 10 µg and 20 µg doses, respectively (Allen 2010). This inverse relationship is likely because excess vitamin B12 (i.e., greater than 2 µg vitamin B12) undergoes an inefficient passive, non-specific absorption process, where only 1-2% of the excess dose is absorbed (EFSA 2015; Carmel 2020).

Following absorption in the gastrointestinal tract, vitamin B12 relies on various proteins to be

[1] The EFSA (2017) reported a conservative absorption estimate of 40% based on a systematic review conducted by Doets et al. (2013); however, the EFSA noted that this analysis had limitations including uncertainties in the available estimates of vitamin B12 absorption.

transported throughout the body, as it cannot cross membranes efficiently (Carmel 2020). The free vitamin B12 binds to various proteins, such as haptocorrin and intrinsic factor protein, as it travels through the gastrointestinal system. Vitamin B12 released from the intrinsic factor protein is metabolized to methylcobalamin or deoxyadenosyl-derivatives. The methylcobalamin metabolites are primarily found in serum bound to transcobalamin which facilitates transport to the cells (EFSA 2015; Watanabe 2007; Allen 2010). Approximately 50% of the available serum vitamin B12 metabolites (primarily as 5′-deoxyadenosylcobalamin but also lower amounts of hydroxycobalamin) are transported to the liver, while the remaining are taken to other tissues but do not accumulate (EFSA 2015). Metabolized vitamin B12 is secreted in bile and can be reabsorbed if bound to the intrinsic factor protein. Absorbed vitamin B12 is also largely excreted in the feces and, when circulating cobalamin exceeds the plasma binding capacity, the excess is excreted in the urine (IOM 1998; EFSA 2015).

Safety Considerations

There are no known adverse effects associated with the consumption of vitamin B12 from foods or supplements (SCF 2000; IOM 1998; EVM, 2003; Drake 2023). At the time of CRN's 3rd edition, as well as reviews by authoritative agencies (e.g., the IOM (1998), the SCF (2000), and the EVM (2003); see *Official Reviews*), only a small number of human clinical studies conducted with oral vitamin B12 were available, all of which consistently demonstrated a lack of adverse effects. These earlier studies demonstrated that oral supplementation with vitamin B12 doses ranging from 300 to 6,000 µg per day administered from two months up to three years did not produce any adverse effects or did not mention observing any adverse effects (Maeda et al. 1992; Waife et al. 1963; Berlin et al. 1968; Juhlin and Olsson 1997; Takahashi et al. 1999). In one small, multicenter trial, two different protocols were followed to treat sleep-waking rhythm disorders in 13 patients with no mention of whether adverse effects were assessed or observed (Maeda et al 1992). First, in the double-blind, placebo-controlled protocol, vitamin B12 (3,000 µg per day) or placebo was administered to four subjects for 8 weeks, followed by 1,500 µg per day in all subjects for an additional undefined period of time. Ten other cases were given 1,500 µg vitamin B12 per day for the total time period (Maeda et al. 1992). In a separate clinical trial, patients with vitiligo (n=100) were orally treated with 5 mg folic acid and 2,000 µg per day vitamin B12 (1,000 µg twice a day) for three months. The study did not mention whether the authors assessed for or

observed any adverse effects; however, 27 patients stopped taking the supplement after one to two months and 48 stopped taking the supplement after three to six months, and the reasons for withdrawal were not provided (Juhlin and Olsson 1997). The third most relevant study from previous reviews was a double-blind trial in which patients with sleep-wake rhythm disorders were orally treated with 30 µg per day (as a control)[2] or 6,000 µg vitamin B12 per day for eight weeks (Takahashi et al. 1999).[3] While there was no mention of whether adverse effects were assessed or observed, the authors stated that the physical condition of participants was "significantly improved."

Fifty-three human clinical trials published since the 3rd edition (i.e., 2014) were identified that met the inclusion criteria (see CRN Methodology Chapter).[4] As described above, no adverse effects attributed to oral vitamin B12 had previously been reported in clinical trials. Consistent with previous findings, no serious adverse effects associated with vitamin B12 were reported across the 53 studies identified in this update, in which vitamin B12 doses ranged from 1 to 1,000,000 µg per day. In addition, excess vitamin B12 is known to be efficiently excreted and does not accumulate in the body. Given the lack of any adverse effects associated with vitamin B12 in human clinical trials, studies at higher dose levels (i.e., 1,500 µg vitamin B12 per day or higher) are most relevant to the previous CRN UL and are summarized below for the purposes of this update.[5]

Of the 53 studies identified, 13 tested doses of 1,500 µg vitamin B12 per day or higher. While no serious adverse effects were reported, not all studies were designed to specifically assess adverse effects. In one study, Erfani et al. (2023) orally administered 1,000,000 µg vitamin B12 per day to patients (n=34) with confirmed COVID-19 for seven days; the study did not mention whether adverse effects were assessed or observed. Mansour et al. (2026) orally dosed patients with diabetic peripheral neuropathy (n=35) with either 1,000 or 2,000 µg vitamin B12 per day for 16 weeks with no adverse changes in metabolic or hematologic parameters assessed. Naik et al.

[2] This study used a low dose (30 µg) of vitamin B12 as a placebo control, which was confirmed not to increase blood vitamin B12 levels.
[3] Takahashi et al. (1999) does not clearly state the route of administration of vitamin B12. However, the EFSA noted it to be oral exposure in *The EFSA Journal* (2008) 815, 1-21.
[4] Literature search conducted May 2026
[5] Consistent with CRN's chapter updates, a full literature review is outside the scope of this chapter.

(2026) dosed pregnant women (n=141) with 5,000 µg vitamin B12 per day for 14 days before the women were administered one of three treatments (milk containing 1.6 µg vitamin B12 per day, pills containing 1.6 µg vitamin B12 per day, or placebo) until they were four months postpartum. This study did not mention if adverse effects were assessed or observed. Six studies administered oral doses of vitamin B12 at a dose of 1,500 µg per day for durations ranging from 6 to 12 weeks, all reporting that no adverse effects occurred (Han et al. 2017; Peng and Gong 2021; Yamasaki et al. 2022; Gao et al. 2024; Aoyama et al. 2022; Zhang et al. 2021). An additional four studies administered oral vitamin B12 at a dose of 1,500 µg per day for 1 to 3 months with no mention of whether side effects were assessed or reported (Kuroki et al. 2015; Hirayama et al. 2015; Ueno et al. 2022; Chauhan et al. 2018).

Official Reviews

IOM (1998). The IOM (1998) reported that "no adverse effects have been associated with excess [vitamin] B12 intake from food or supplements in healthy individuals." However, the dietary intake levels of vitamin B12 at that time were reported by the IOM to range from 3-7 µg per day in the United States and Canada (i.e., well below levels currently used in dietary supplements). The IOM review did not include any study investigating oral supplementation with vitamin B12. However, its review included parenteral studies involving administration of vitamin B12 to patients with pernicious anemia with no reports of any adverse effects (Boddy and Adams 1968; Mangiarotti et al. 1986; Martin et al. 1992). The IOM reported that only small amounts of vitamin B12 are absorbed in the gastrointestinal tract when high oral doses are administered, potentially explaining the "apparent low toxicity." The IOM concluded that the available studies were not "considered sufficient for a dose-response assessment and derivation of a UL."

European Commission's Scientific Committee on Food (EC SCF 2000). The EC SCF (2000) also reported that "no adverse effects have been associated with excess vitamin B12 intake from food or supplements in healthy individuals." Oral supplementation with doses ranging from 300 to 3,000 µg per day administered for 8 weeks to up to 3 years did not produce any adverse effects (Berlin et al. 1968; Maeda et al. 1992). However, the EC SCF noted that these studies were not designed to find adverse effects. The EC SCF concluded that "there are no clearly defined adverse effects produced by vitamin B12 that can be used to define a LOAEL or NOAEL, which can be

used as a basis for deriving a UL." As such, no UL was determined by the EC SCF (2000). Of note, in 2015, the EFSA provided a scientific opinion on the dietary reference values for vitamin B12 but did not introduce nor discuss any new safety data regarding ingestion of vitamin B12. Instead, the EFSA (2015) cited the conclusions of the EC SCF (2000). In 2009, EFSA provided a scientific opinion on a vitamin B12-enriched yeast, but this opinion did not include a risk assessment for vitamin B12 since the data were not "suitable" to assess bioavailability or safety.

EVM (2003). The UK's EVM found no evidence of adverse effects of vitamin B12 in humans. According to the EVM, no adverse effects were reported in several studies that orally administered vitamin B12 at doses of 300 µg to 6,000 µg per day over periods spanning from 2 to 70 months (Waife et al 1963; Berlin et al 1968; Juhlin and Olsson 1997; Takahashi et al 1999[6]). The EVM concluded that the available data were insufficient to set a SUL for vitamin B12. Therefore, the EVM set a supplemental guidance level of 2,000 µg per day based on Juhlin and Olsson (1997), which reported no adverse effects during the 12-month study.

Chinese Nutrition Society (CNS 2023). The CNS determined recommended nutrient intake (RNI) levels for vitamin B12 but did not derive ULs.[7]

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). The ICMR-NIN concluded "no TUL identified" for vitamin B12.[8]

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. The KNS determined AI levels for vitamin B12 but did not derive ULs.[9]

CRN Recommendations

CRN previously developed a supplemental UL of 3,000 µg per day. The goal of the current chapter was to determine whether more recent human clinical data are available that might impact

[6] EVM states that "the route of administration was not clear from the information given" in the study.
[7] No additional information was provided.
[8] No additional information was provided.
[9] Table 4 of KNS (2020) states that vitamin B12 was included in the 2020 update to update the RNI and EAR only.

the conclusions published in the 3rd edition. While not all human clinical trials reviewed were specifically designed to evaluate adverse effects, no trials were identified following CRN's updated methodology that reported any serious adverse effects associated with vitamin B12 supplementation. Following CRN's methodology (see Methodology Chapter), and due to the lack of any known adverse effects for vitamin B12, an HOI was established by CRN in this update. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the HOI are recognized.

CRN's safety methodology for deriving supplemental HOI values prioritizes data from human studies, when available. Fifty-three human clinical trials published since 2014 were identified and subsequently reviewed that met the inclusion criteria for the current chapter. The table below summarizes the key human clinical studies considered in deriving a supplemental HOI value by CRN according to its principal points of departure for risk assessment (as described in the Methodology Chapter).[10]

[10] Where numerous relevant studies were identified, those most pertinent to the UL/HOI derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the UL and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

Studies Considered for the CRN HOI for Vitamin B12 in Adults

Reference	Study Design	Participant Description	No. of Subjects	Supplemental Dose(s) (µg/day)	Duration	NOAEL (µg/day)
Key studies from 3rd edition and official reviews						
Maeda et al. 1992	Multicenter; double-blind, placebo-controlled	Patients with sleep-waking rhythm disorders	4	0, 3,000 followed by 1,500	>2 months[a]	3,000
	Multicenter		10	1,000	>2 months[b]	1,500
Juhlin and Olsson 1997	Clinical	Patients with vitiligo	100	2,000[c]	3 months	2,000
Takahashi et al. 1999	Double-blind	Patients with sleep-waking rhythm disorders	51	30, 6,000[d]	2 months	6,000
Key studies identified in update						
Erfani et al. 2023	Randomized, placebo-controlled	Patients with confirmed COVID-19	34	0, 1,000,000	7 days	1,000,000
Mansour et al. 2026	Randomized	Adults with diabetic peripheral neuropathy	35	1,000, 2,000	4 months	2,000
Naik et al. 2026	Randomized, longitudinal	Pregnant women deficient in vitamin B12	141	5,000 followed by 0 or 1.6[e]	14 days and then until 4 months postpartum	5,000

[a] Vitamin B12 (3,000 µg per day) or placebo was administered to four subjects for 8 weeks, followed by 1,500 µg per day in all subjects for an additional undefined period of time.
[b] Total duration was unclear from publication.
[c] This study is a co-exposure study that administered 2,000 µg vitamin B12 (1,000 µg twice per day) and 10 mg folic acid daily. The study is included here because a previous EVM opinion utilized this study to assist in setting the guidance level.
[d] This study used a low dose (30 µg) of vitamin B12 as a placebo control, which was confirmed not to increase blood vitamin B12 levels.
[e] This study recruited women before week 17 of pregnancy and divided into three groups, all primed for 14 days with oral 5,000 µg vitamin B12 per day. Afterwards, the participants received 400 ml of milk (vitamin B12 = 1.6 µg; n = 31), vitamin B12 pills (vitamin B12 = 1.6 µg; n = 32), or placebo (n = 13) until 4 months postpartum.

Supplemental ULs for vitamin B12 have not been established by authoritative agencies, such as the IOM (1998), the SCF (2000), and the EVM (2003), due to the lack of sufficient data to conduct a risk assessment (see *Official Reviews*). However, each of these agencies noted the lack of any adverse effects associated with excess vitamin B12 in available clinical studies. In addition, the EVM (2003) set a supplemental guidance level of 2,000 µg per day based on the Juhlin and Olsson (1997) study.

In its 3rd edition, CRN concurred with the authoritative agencies that there is a lack of adverse effects observed at any level of vitamin B12 intake. At that time, CRN developed a supplemental UL of 3,000 µg per day based on clinical evidence of safety at oral intakes at that dose,[11] while also noting the clinical trial by Juhlin and Olsson (1997) at 2,000 µg per day. Additional human clinical studies published since the 3rd edition were identified as part of this update administered vitamin B12 at doses up to 1,000,000 µg per day. No side effects were reported in any trial identified; however, not all studies were specifically designed to assess such. Of the available clinical trials identified, the four conducted with oral doses ranging from 3,000 to 1,000,000 µg per day support the previously set CRN UL of 3,000 µg vitamin B12 per day (Maeda et al. 1992; Takahashi et al. 1999; Erfani et al. 2023; Naik et al. 2026). However, each of these studies has limitations in design that preclude its utility to identify a NOAEL for the purposes of deriving a new UL (or HOI). These limitations include lack of placebo control (Naik et al. 2026), small study size (e.g., Maeda et al. 1992), and short duration (Naik et al. 2016; Erfani et al. 2023). In addition, none of these four studies specifically assessed or observed adverse effects (and none were reported). Taken together, these studies support the previous CRN UL but do not provide sufficient evidence to justify selection of a higher NOAEL and, therefore, derivation of a higher HOI (or UL).

CRN (2014) previously established a supplemental UL of 3,000 µg per day for vitamin B12. As reviewed in this update, no new data have become available that identify any serious adverse effects in clinical trials with vitamin B12, including at doses at and above the existing CRN UL. In

[11] No specific studies were described to support this statement in CRN's 3rd edition. Rather, data as reviewed by the IOM (1998), the SCF (2000), and the EVM (2003) were relied on.

addition, excess vitamin B12 is known to be efficiently excreted and does not accumulate in the body. Based on the available dataset, the previous UL derived by CRN is carried forward to establish a supplemental HOI of 3,000 µg vitamin B12 per day for adults, as no serious adverse effects have been identified for this nutrient.[12]

Quantitative Summary for Vitamin B12 in Adults

CRN (2026) HOI, supplemental intake	3,000 µg (3 mg)/day
IOM (1998) UL, total intake	Not determined
EC SCF (2000) UL, total intake	Not determined
EVM (2003), guidance level, supplemental intake	2,000 µg (2 mg)/day
CNS (2023), total intake	Not determined
ICMR-NIN (2020), total intake	Not determined
KNS (2020), total intake	Not determined
CNS (2023), total intake	Not determined

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[12] No specific NOAEL was identified for vitamin B12, thus no UFs are applied. Instead, the previous UL value is maintained but established as an HOI due to the absence of any serious adverse effects.

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