

Vitamin B₆ (Pyridoxine)

Common Acronyms

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
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Vitamin B₆ is a water-soluble vitamin that is important in carbohydrate, lipid, and amino acid metabolism. It is found in the body in three primary forms: pyridoxine (the common name given mainly to the alcohol form, or pyridoxol); pyridoxal (the aldehyde); and pyridoxamine (the amine). The activated forms of pyridoxal and pyridoxamine are active coenzyme forms, and the interconversion between them is involved in many of the biological functions of vitamin B₆. This vitamin is extensively involved in the metabolism of nitrogen-containing compounds, including serotonin, dopamine, norepinephrine, gamma-aminobutyric acid (GABA), and the heme

component of hemoglobin. Pyridoxine, as pyridoxal phosphate, also has an important role in the conversion of tryptophan to nicotinic acid.

Vitamin B₆ interacts with several drugs, which may either decrease the activity of the drug and/or increase the need for the vitamin. Individuals taking medications on a regular basis should discuss their vitamin B₆ status with their health care providers. Furthermore, several medical conditions, including autoimmune disorders, impaired renal function, and alcohol dependence, can increase the requirement for pyridoxine (IOM 1998; Bates 1999; Chiang 2005).

Safety Considerations

Both deficiency and excess of pyridoxine may produce neurological disturbances (Hathcock and Rader 1990; Muhamed et al. 2023; Cracknell et al. 2024). The first report of pyridoxine neurotoxicity in humans described a sensory neuropathy of the extremities in women with daily intakes of 2,000 to 6,000 mg, mostly taken to control premenstrual symptoms (Schaumburg et al. 1983). The neuropathy slowly and often incompletely regresses after cessation of the elevated dose (Albin et al. 1987; Albin and Albers 1990; Santoro et al. 1991). Most cases of sensory neuropathy have resulted from intakes of greater than 600 mg per day, but evidence suggests that for some individuals, neuropathy may occur after doses as low as 300 to 500 mg (Parry and Bredesen 1985; Bendich and Cohen 1990; Hathcock and Rader 1990). At high intake levels, the total dose over time may give a better prediction of the potential for neurotoxic response than either the daily dose or the duration of the high intake (Bendich and Cohen 1990). More recent Dutch, French, and Finnish vigilance system data published or submitted to EFSA have reported individual cases of intake levels below 100 mg per day of pyridoxine and peripheral neuropathy (van Hunsel et al. 2018; Vrolijk et al. 2020; EFSA 2023). As noted by EFSA (2023), such self-reported case study data have inherent limitations in their utility in establishing a causal association.

Treatment with either 150 or 300 mg of pyridoxine for up to 4 months did not produce signs of sensory neuropathy or any other adverse effects in 24 carpal tunnel syndrome patients (Del

Tredici et al. 1985). Bernstein and colleagues (Bernstein and Lobitz 1988; Bernstein and Dinesen 1993), using physical neurological methods, found no evidence of neurological effects of pyridoxine at intakes of up to 200 mg per day over a period of 4 months. Most subjects showed no adverse effects at 150 to 200 mg per day supplemental intake (Del Tredici et al. 1985; Parry and Bredesen 1985; Bernstein and Lobitz 1988; Bernstein and Dinesen 1993). At intakes of 200 mg (but not at 150 mg), a few subjects experienced signs of adverse neurological effects such as sensory tingling and numbness (Parry and Bredesen 1985; Brush 1988). Consumption of 200 mg pyridoxine per day may decrease the time it takes for adverse effects to develop after higher levels are initiated (Parry and Bredesen 1985). Of note, 11 cases of 336 total subjects reported related effects (dizziness = 5, mild tingling = 6) in a follow-up report after three additional years in this cohort (EC SCF 2000; EFSA 2023). Similar findings were reported in a more recent retrospective case control study in which 200 mg per day pyridoxine for up to 18 months was associated with symptoms of peripheral neuropathy in some subjects (Alsabah et al. 2017).

Available human clinical trials with pyridoxine intervention levels of 100 mg per day have demonstrated a lack of adverse effects in participants. Cracknell et al. (2024) reported the outcome of a trial assessing sensory reactivity in 300 participants from the general population. No symptoms of neuropathy or any other adverse effects were observed following ingestion of 100 mg per day for 30-40 days in this study. In a double-blind, placebo-controlled study in which 100 or 500 mg of vitamin B₆ was consumed daily for 14 days, marginal evidence of improvement in a digital coding test but also some evidence of an adverse effect on word recognition was shown (Molimard et al. 1980); no further evidence to support either of these possible effects has been published. The apparent adverse effect was significant at a 500 mg intake level, but not at 100 mg in this study. It is unclear whether the duration of exposure to pyridoxine in the latter study was sufficient to account for development of neuropathy symptoms as the time to onset of symptoms has been shown to vary, though generally occur following longer durations at lower levels. For example, a more recent prospective study demonstrated that the median time to peripheral neuropathy in subjects was 38.5-43 days, with intake levels of 200 and 150 mg per day, respectively (Court et al. 2021).

Some recent clinical studies with very high doses of pyridoxine have reported a lack of adverse

effects following intakes of 350-2,100 mg per day for up to one year (Hoyer-Kuhn et al. 2014; Tanigawa et al. 2021). However, the small number of participants in these studies limits their utility for hazard identification. Inter-individual differences in sensitivity to pyridoxine-induced peripheral neuropathy have been demonstrated and are considered to account for at least some of the variability in response observed across studies with different pyridoxine doses (Vrolijk et al., 2020; Hadtstein and Vrolijk 2021).

There is strong controversy over the validity of the study reporting adverse effects at daily pyridoxine intakes of approximately 100 mg or less (Dalton and Dalton 1987). The design of the study, which involved telephone interviews using leading questions, has raised questions about the validity of its observed effects. Although the Dalton and Dalton report has been cited as evidence that pyridoxine intakes below 100 mg per day can cause sensory neuropathy (EC SCF 2000; EFSA 2023; EVM 2003), the data showed an average intake of 117 mg per day among women with adverse symptoms and a nearly identical average intake (116 mg per day) in the control group. The group with reported symptoms had taken pyridoxine for a longer period of time—an average of 2.9 years, compared with 1.6 years for those without symptoms. Some women reporting adverse effects had intakes of 50 mg or less. Inaccuracies in the telephone survey method and a lack of objective neurological assessment are likely to have introduced bias. The symptoms observed had no dose-response relationship to pyridoxine intake. The IOM concluded that the data were not of sufficient quality to warrant use in a risk assessment for pyridoxine (IOM 1998).

Official Reviews

IOM (1998). The IOM identified a NOAEL of 200 mg from clinical data (Del Tredici et al. 1985; Bernstein and Lobitz 1988) but considered the Dalton and Dalton (1987) data too unreliable to serve as the basis of a UL. It thus applied a UF of 2 to the 200 mg human NOAEL, deriving a UL of 100 mg.

EFSA (2023). Previously, EC SCF (2000) identified a LOAEL of 100 mg per day from the Dalton and Dalton (1987) study. However, in 2023, the EFSA Panel concluded that a LOAEL and NOAEL

could not be identified from human studies. Instead, the Panel identified a “reference point” of 50 mg per day based on the same study. The Panel supported this reference point with data from other case reports as well as vigilance data, which were also described by the Panel as being “limited and mostly insufficient to verify a causal link.” The Panel divided this reference point (50 mg per day) by a composite UF of 4 to account for the inverse relationship between dose and time and a further factor of 2 to allow for deficiencies in the database, thus yielding a UL of 12.5 mg per day for pyridoxine. A UL value was also calculated by the Panel based on the subchronic study in Beagle dogs (Phillips et al., 1978). The LOAEL of 50 mg per kg body weight per day from this study was divided by a composite UF of 300, yielding a UL of 11.7 mg per day based on a 70-kg adult. The composite UF consisted of factors of 2 and 4 to account for interspecies variability in toxicokinetics and toxicodynamics, respectively, a factor of 10 for interspecies extrapolation, a factor of 2 for subchronic-to-chronic extrapolation, and a factor of 3 to account for the lack of a NOAEL. The Panel noted that the similar UL values resulting from human and animal studies increased confidence in their findings. Based on the midpoint of these values and rounding down, a UL of 12 mg per day for total intake of all vitamin B6 vitamers in adults was identified by the EFSA Panel.

EVM (2003). The UK’s EVM, concluding that the available human data were inadequate, based their assessment on the same LOAEL of 50 mg per kg body weight per day in dogs (Phillips et al. 1978). They extrapolated the dog data to a 60-kg human adult representative weight by applying a composite UF of 300 to derive an SUL of 10 mg per day. The composite factor represented a factor of 3 for LOAEL-to-NOAEL extrapolation, a factor of 10 for interspecies extrapolation, and another factor of 10 for variation in human sensitivity.

Chinese Nutrition Society (CNS 2023). An UL value for pyridoxine of 55-60 mg per day in adults was set by the CNS.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN2020). The ICMR-NIN determined the UL for pyridoxine in adults to be 100 mg per day, based on a review of available literature and citing IOM (1998) and the 3rd edition of the CRN Vitamin and Mineral Safety book.

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting dietary reference intakes (DRIs). Based on this approach, UL values of 100 and 95 mg per day were derived for pyridoxine in adults ages ≥ 19 and 18 years, respectively.

CRN Recommendations

The goal of the current update to CRN's supplemental UL for pyridoxine was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that reported neuropathy-related symptoms or other serious adverse effects associated with pyridoxine intervention.¹ As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized. As discussed above, other methodologies have been used by some government agencies that have relied on older case-control studies, more recent self-reported vigilance data, and/or animal toxicology data to derive associated UL values.

CRN's safety methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The table below summarizes the key human clinical and epidemiological studies considered in deriving an updated UL for supplemental intakes by CRN according to its principal points of departure for risk assessment (as described in the Methods).

¹ Literature search conducted September 2024.

Key Studies Considered for the CRN UL for Vitamin B₆ (Pyridoxine)

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg per day)	Duration	NOAEL (mg/day)	LOAEL (mg/day)
Key studies from 3rd edition							
Brush 1988	Retrospective Survey	Subjects with premenstrual syndrome	630	40-200	<6 months to 5 years	160	200
Parry and Bredesen 1985	Case series	Subjects with neuropathy from vitamin B ₆ abuse	16	200-5,000	1 month to 6 years	N/A	200
Key studies identified in update							
Hoyer-Kuhn et al. 2014	Randomized controlled trial	Patients with primary hyperoxaluria type I	12	350-1,400 ^{a,b}	24 weeks	350-1,400 ^a	N/A
Alasbah et al. 2017	Retrospective case control study	Post-laparoscopic sleeve gastrectomy patients	32	200	≤18 months	N/A	200
Cracknell et al. 2024	Clinical trial	General population	300	100	30-40 days	100	N/A
Tanigawa et al. 2021	Prospective open-label multicenter pilot study	Patients with inherited glycosylphosphatidylinositol deficiencies	9	700-2,100 ^{a,c}	1 year	700-2,100 ^a	N/A

N/A, not applicable

^a Dose converted based on 70-kg adult

^b 5 mg per kg body weight every 6 weeks, up to a final dosage of 20 mg per kg body weight per day at week 24

^c 10 mg per kg body weight per day for two weeks, then 30 mg per kg body weight per day for up to one year

While some case studies have reported effects at lower doses (e.g., Dalton and Dalton 1987), the complete absence of adverse effects in credible, well-designed human studies at 100, 150, and up to 160 mg per day and only marginal evidence of adverse effects at 200 mg (Parry and Bredenson 1985; Brush 1988; Alasbah et al. 2017; Cracknell et al. 2024) indicate that 100 mg can be confidently identified as a safe level of consumption based on studies in the table above. Following the CRN process, the supplemental intake of 100 mg per day reported in the recent human clinical trial by Cracknell et al. (2024) is identified as the NOAEL for pyridoxine. This NOAEL is supported by additional studies reporting a lack of adverse effects with higher doses

of pyridoxine, longer interventions, and/or larger population sizes; the latter of which also provides additional confidence, considering inter-individual differences in sensitivity have been demonstrated for pyridoxine-induced peripheral neuropathy. As described in the Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN’s methodology, an UF of 1 is applied to yield a UL of 100 mg per day for adults for pyridoxine.

Quantitative Summary for Vitamin B₆ (Pyridoxine) for Adults

CRN (2024) UL, supplemental intake	100 mg/day
IOM (1998) UL, total intake	100 mg/day
EFSA (2023) UL, total intake	12 mg/day
EVM (2003) SUL, supplemental intake	10 mg/day
CNS (2023), total intake	55-60 mg/day
ICMR-NIN (2020), total intake	100 mg/day
KNS (2020), total intake	100 mg/day (95 mg/day for ages 15-18 years)

References

Alsabah A, Al Sabah S, Al-Sabah S, Al-Serri A, Al Haddad E, Renno WM. 2017.

Investigating Factors Involved in Post Laparoscopic Sleeve Gastrectomy (LSG)

Neuropathy. *Obes Surg.* 27(5):1271-1276.

Albin RL, Albers JW. 1990. Long-term follow-up of pyridoxine-induced acute sensory neuropathy-neuronopathy. *Neurology.* 40:1319.

Albin RL, Albers JW, Greenberg HS, et al. 1987. Acute sensory neuropathy-neuronopathy from pyridoxine overdose. *Neurology.* 37:1729–1732.

Bates CJ, Pentieva KD, Prentice A. 1999. An appraisal of vitamin B₆ status indices and associated confounders, in young people aged 4–18 years and in people aged 65 years and over, in two national British surveys. *Public Health Nutr.* 2:529–535.

Bendich A, Cohen M. 1990. Vitamin B₆ safety issues. *Ann NY Acad Sci.* 585:321–323.

Bernstein AL, Dinesen JS. 1993. Effect of pharmacologic doses of vitamin B₆ on carpal tunnel syndrome, electroencephalographic results, and pain. *J Am College Nutr.* 12:73–76.

Bernstein AL, Lobitz CS. 1988. A clinical and electrophysiologic study of the treatment of painful diabetic neuropathies with pyridoxine. In: Leklem JE, Reynolds RD, eds. *Clinical and Physiological Applications of Vitamin B-6*. New York: Liss; 415–423.

Brush MG. 1988. Vitamin B-6 treatment of premenstrual syndrome. In: Leklem JE, Reynolds RD, eds. *Clinical and Physiological Applications of Vitamin B-6*. New York: Liss; 363–379.

Chiang EP, Selhub J, Bagley PJ, et al. 2005. Pyridoxine supplementation corrects vitamin B₆ deficiency but does not improve inflammation in patients with rheumatoid arthritis. *Arthritis Res Ther.* 7:R1404–R1411.

Chinese Nutrition Society (CNS). 2023. Dietary Reference Intakes for China, A summary Report. People's Medical Publishing House.

Court R, Centner CM, Chirehwa M, Wiesner L, Denti P, de Vries N, Harding J, Gumbo T, Maartens G, McIlleron H. 2021. Neuropsychiatric toxicity and cycloserine concentrations during treatment for multidrug-resistant tuberculosis. *Int J Infect Dis.* 105:688–694.

Cracknell RO, Tavassoli T, Field DT. 2024. High-dose Vitamin-B6 reduces sensory over-responsivity. *J Psychopharmacol.* 24:2698811241271972.

Curhan GC, Willett WC, Rimm EB, Stampfer MJ. 1996. A prospective study of the intake of

vitamins C and B₆, and the risk of kidney stones in men. *J Urol*. 155:1847–1851.

Dalton K, Dalton MJT. 1987. Characteristics of pyridoxine overdose neuropathy syndrome. *Acta Neurol Scand*. 76:8–11.

Daudon M, Reveillaud RJ, Normand M, Petit C, Jungers P. 1987. Pyridoxilate-induced calcium oxalate calculi: a new drug-induced metabolic nephrolithiasis. *J Urol*. 138:258–261.

Del Tredici AM, Bernstein AL, Chinn K. 1985. Carpal tunnel syndrome and vitamin B-6 therapy. In: Reynolds RD, Leklem JE, eds. *Vitamin B-6: Its Role in Health and Disease*. New York: Liss; 459–462.

European Commission, Scientific Committee on Food (EC SCF). 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B₆. European Commission, SCF/CS/NUT/UPPLEV/16 Final Report. Brussels.

European Food Safety Authority (EFSA) NDA Panel (Panel on Nutrition, Novel Foods and Food Allergens), Turck D, Bohn T, Castenmiller J, de Henauw S, Hirsch-Ernst K-I, Knutsen HK, Maciuk A, Mangelsdorf I, McArdle HJ, Pelaez C, Pentieva K, Siani A, Thies F, Tsabouri S, Vinceti M, Fairweather-Tait S, Vrolijk M, Fabiani L, Titz A and Naska A. 2023. Scientific opinion on the tolerable upper intake level for vitamin B6. *EFSA Journal*. 21(5):8006, 110 pp.

Expert Group on Vitamins and Minerals (EVM), Committee on Toxicity. 2003. *Safe Upper Levels for Vitamins and Minerals*. London: Food Standards Agency Publications.

Hadtstein F, Vrolijk M. 2021. Vitamin B-6-Induced Neuropathy: Exploring the Mechanisms of Pyridoxine Toxicity. *Adv Nutr*. 12(5):1911-192.

Hathcock JN, Rader JJ. 1990. Micronutrient safety. *Ann NY Acad Sci*. 587:257–266.

Hoyer-Kuhn H, Kohbrok S, Volland R, Franklin J, Hero B, Beck BB, Hoppe B. 2014. Vitamin B6 in primary hyperoxaluria I: first prospective trial after 40 years of practice. *Clin J Am Soc*

Nephrol. 9(3):468-77.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN). 2020. *ICMR-NIN Expert Group on Nutrient Requirement for Indians, Recommended Dietary Allowances (RDA) and Estimated Average Requirements (EAR)*.

Institute of Medicine (IOM). 1998. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press.

Korean Nutrition Society (KNS). 2020. Ministry of Health and Welfare (KR). The Korean Nutrition Society. *Dietary Reference Intakes for Koreans*. Sejong: Ministry of Health and Welfare.

Leklem JE. 1994. Vitamin B₆. In: Shils ME, Olson JA, Shike M, eds. *Modern Nutrition in Health and Disease*. 8th ed. Philadelphia: Lea and Febiger; 383–394.

Molimard R, Marillaud A, Paille A, Le Devehat C, Lemoine A, Dourgny M. 1980. Impairment of memorization by high doses of pyridoxine in man. *Biomedicine*. 32:88–92.

Muhamad R, Akrivaki A, Papagiannopoulou G, Zavridis P, Zis P. 2023. The Role of Vitamin B6 in Peripheral Neuropathy: A Systematic Review. *Nutrients*. 15(13):2823.

Parry GJ, Bredesen DE. 1985. Sensory neuropathy with low-dose pyridoxine. *Neurology*. 35:1466–1468.

Phillips WEJ, Mills JHI, Charbonneau SM, et al. 1978. Sub-acute toxicity of pyridoxine hydrochloride in the beagle dog. *Toxicol Appl Pharmacol*. 44:323–333.

Santoro L, Ragno M, Nucciotti R, Barbieri F, Caruso G. 1991. Pyridoxine neuropathy: a four year electrophysiological and clinical follow-up of a severe case. *Acta Neurol*. 13:13–18.

Schaumburg H, Kaplan J, Windebank A, et al. 1983. Sensory neuropathy from pyridoxine abuse. *N Engl J Med.* 309:445–448.

Tanigawa J, Nabatame S, Tominaga K, Nishimura Y, Maegaki Y, Kinoshita T, Murakami Y, Ozono K. 2021. High-dose pyridoxine treatment for inherited glycosylphosphatidylinositol deficiency. *Brain Dev.* 43(6):680-687.

van Hunsel F, van de Koppel S, van Puijenbroek E and Kant A. 2018. Vitamin B(6) in health supplements and neuropathy: Case series assessment of spontaneously reported cases. *Drug Safety.* 41:859–869.

Vrolijk MF, Hageman GJ, van de Koppel S, van Hunsel F and Bast A. 2020. Inter-individual differences in pharmacokinetics of vitamin B6: A possible explanation of different sensitivity to its neuropathic effects. *PharmaNutrition.* 12:100188.

Wen YF, Zhao JQ, Bhadauria M, Nirala SK. 2010. Pyridoxine mitigates cadmium induced hepatic cytotoxicity and oxidative stress. *Environ Toxicol Pharmacol.* 30:169–174.

Updated July 2025