

## **Vitamin B<sub>6</sub> (Pyridoxine)**

---

### *Function*

Vitamin B<sub>6</sub> in blood and tissues occurs phosphorylated in three primary forms: pyridoxine (the alcohol 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 the vitamin. This vitamin is extensively involved in the metabolism of amino acids and other nitrogen-containing compounds, and also in the metabolism of lipids and the production and activities of certain hormones. Pyridoxine, as pyridoxal phosphate, has an important role in the conversion of tryptophan to nicotinic acid. Increasing protein intake increases the requirement for pyridoxine (Leklem 1999).

Vitamin B<sub>6</sub> interacts with several drugs, which may either decrease the activity of the drug or increase the need for the vitamin, or both. In most cases, increasing vitamin B<sub>6</sub> intake to about 10 mg per day corrects the nutritional aspects of these interactions, but the possible impact of high intake of vitamin B<sub>6</sub> on drug efficacy should be considered (Leklem 1999).

### **Safety Evidence**

Both deficiency and excess of pyridoxine may produce neurological disturbances (Hathcock and Rader 1990). 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 in an attempt to control premenstrual symptoms (Schaumburg et al. 1983). The neuropathy slowly and perhaps 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; Hathcock and Rader 1990; Bendich and Cohen 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). This relationship does not extend to low, nontoxic doses.

Treatment with either 150 or 300 mg of pyridoxine for up to four months did not produce signs of sensory neuropathy or any other adverse effects in twenty-four carpal tunnel syndrome patients (Del Tredici et al. 1985). Bernstein and coworkers (Bernstein and Lobitz 1988; Bernstein and Dinesen 1989), 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 four months.

Most subjects showed no adverse effects at a 150 to 200 mg per day supplemental intake (Bernstein and Lobitz 1988; Bernstein and Dinesen 1989; Parry and Bredesen 1985; Del Tredici et al. 1985). 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).

A double-blind, placebo-controlled study in which 100 or 500 mg of vitamin B<sub>6</sub> was consumed daily for fourteen days showed marginal evidence of improvement in a digital coding test, but also some evidence of an adverse effect on word recognition (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.

There is strong controversy over the validity of the single study reporting adverse effects at daily pyridoxine intakes of around 100 mg or less (Dalton and Dalton 1987). The design of the study, which involved telephone interviews using leading questions, has raised doubts 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 (Scientific Committee on Food 2000; Expert Group on Vitamins and Minerals 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, but they apparently showed a time-response relationship. The FNB concluded that the data were not of sufficient quality to warrant use in a risk assessment for pyridoxine (Food and Nutrition Board 1998).

Some reports have suggested that high intakes of pyridoxine may carry risk of oxalate kidney stones. Such concerns seem unfounded. The reported cases may have been associated with the drug pyridoxilate (a combination of pyridoxine and glyoxalate) (Daudon et al. 1987), and a recent prospective epidemiological study found the relative risk of oxalate renal stones to be decreased for men consuming

more than 40 mg of pyridoxine in comparison with those consuming less than 3 mg (Curhan et al. 1996).

## **Published Official Reviews of Vitamin B<sub>6</sub> (Pyridoxine) Safety**

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

While EC SCF recognized (Scientific Committee on Food 2000) the weaknesses of the Dalton and Dalton data, it considered the other available clinical data to be of marginal scientific quality as well. Consequently, EC SCF used the Dalton and Dalton data as the basis of its pyridoxine UL, dividing an intermediate LOAEL of 100 mg per day by a composite UF of 4. This 100 mg LOAEL was formulated from the intakes of the Dalton and Dalton group with adverse effects, which consumed a mean intake of 117 mg and a median intake of <100 mg. (The Dalton and Dalton report asserted that some individuals with minor adverse effects had taken only 50 mg per day, but this was not factored into EC SCF's LOAEL.) The composite UF of 4 resulted from assigning a factor of 2 to account for long-term intakes, and a further factor of 2 to allow for deficiencies in the database. The EC SCF thus calculated a UL of 25 mg, which is further justified by the absence of any reports, even anecdotal ones, of adverse effects at intakes of 25 mg.

The UK EVM, concluding that all the available human data were inadequate, derived an SUL of 10 mg per day—for a 60 kg adult representative weight—by applying a composite UF of 300 (Expert Group on Vitamins and Minerals 2003) to a LOAEL of 50 mg per kg body weight per day in dogs (Phillips et al. 1978). 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.

In summary, these three government reports selected three separate sets of data as the critical data set to serve as the basis of their risk assessments. These reports also accounted for uncertainty in three different ways. Not surprisingly, the amounts of pyridoxine considered safe differ accordingly: 100 mg for FNB, 25 mg for EC SCF, and 10 mg for UK EVM. These disparate outcomes suggest that some of the data selections, uncertainty assessments, and corresponding UL values are arbitrary.

## **CRN ULS for Vitamin B<sub>6</sub> (Pyridoxine)**

There is marginal evidence suggesting possible adverse neurological effects at intakes of 200 mg, but not at 100 or 150 mg (Brush 1988; Parry and Bredesen 1985). Consequently, CRN identifies the human supplemental intake NOAEL for pyridoxine to be 100 mg. The absence of adverse effects in most, but not all, studies at 200 mg intake—together with the absence of significant adverse effects at 100 or 150 mg—strongly reduces the uncertainty about the safety of pyridoxine at 100 mg supplemental intake. Intakes from conventional foods alone are generally below 3 mg (Food and Nutrition Board 1998; Expert Group on Vitamins and Minerals 2003), and thus this source does not meaningfully contribute to safety concerns.

The complete absence of adverse effects in credible, well-designed studies at 100 and 150 mg indicates that 100 mg can be confidently identified, with a low level of uncertainty, as a safe level of consumption. Intakes from conventional foods are almost always less than 4 mg per day (Expert Group on Vitamins and Minerals 2003)—a minor amount compared with the maximum safe level—leading CRN to identify 100 mg as the ULS for pyridoxine. Somewhat higher amounts may be safe for most people.

### **Comparison of Safety Values for Vitamin B<sub>6</sub> (Pyridoxine)**

<b>CRN ULS</b>	100 mg
<b>US FNB UL</b>	100 mg
<b>EC SCF UL, supplement intake</b>	25 mg (based on Dalton and Dalton data)
<b>EC supplement maximum</b>	Not established (as of May 2004)
<b>UK EVM SUL, chronic supplement intake</b>	10 mg (extrapolated from animal data)

### *References*

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

Albin RL, Albers JW, Greenberg HS, Townsend JB, Lynn RB, Burke JM, Alessi AG. Acute sensory neuropathy-neuronopathy from pyridoxine overdose. *Neurology* 1987; 37:1729-1732.

Bendich A, Cohen M. Vitamin B<sub>6</sub> safety issues. *Ann of NY Acad Sci* 1990; 585:321-323.

Bernstein AL, Dinesen JS. Effect of pharmacologic doses of vitamin B<sub>6</sub> on carpal tunnel syndrome, electroencephalographic results, and pain. *J Am College Nutr* 1989; 12:73-76.

From: **Vitamin and Mineral Safety 2<sup>nd</sup> Edition** ~ by John N. Hathcock, Ph.D.  
Council for Responsible Nutrition (CRN) All rights reserved. Republication or redistribution of  
content is expressly prohibited without prior written consent of CRN.

Bernstein AL, Lobitz CS. A clinical and electrophysiologic study of the treatment of painful diabetic neuropathies with pyridoxine. In: Clinical and physiological applications of vitamin B-6. New York: Alan R. Liss, 1988; 415-423.

Brush MG. Vitamin B6 treatment of premenstrual syndrome. In: Clinical and physiological applications of vitamin B-6. New York: Alan R. Liss, 1988; 363-379.

Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B<sub>6</sub>, and the risk of kidney stones in men. *J Urol* 1996; 155:1847-1851.

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

Daudon M, Reveillaud RJ, Normand M, Petit C, Jungers P. Pyridoxilate-induced calcium oxalate calculi: A new drug-induced metabolic nephrolithiasis. *J Urol* 1987; 138:2582-61.

Del Tredici AM, Bernstein AL, Chinn K. 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: Alan R. Liss, 1985; 459-462.

Expert Group on Vitamins and Minerals. Safe upper levels for vitamins and minerals, Food Standards Agency, United Kingdom, 2003.

Food and Nutrition Board. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B<sub>6</sub>, folate, vitamin B<sub>12</sub>, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press, 1998.

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

Leklem JE. Vitamin B<sub>6</sub>. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease, 9th ed. Philadelphia: Williams & Wilkins, 1999; 413-421.

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

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

Phillips WEJ, Mills JHI, Charbonneau SM, Tryphonas L, Hatina GV, Zawidska Z, Bryce FR, Munro IC. Sub-acute toxicity of pyridoxine hydrochloride in the beagle dog. *Toxicol Appl Pharmacol* 1978; 44:323-333.

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

Schaumburg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ. Sensory neuropathy from pyridoxine abuse. *N Engl J Med* 1983; 309:445-448.

Scientific Committee on Food. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B<sub>6</sub>. European Commission, SCF/CS/NUT/UPPLEV/16 Final, Brussels, 2000.