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Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin B_6

(expressed on 19 October 2000)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium
Telephone: direct line (+32-2) 29 581.10/659.48/648.70, exchange 299.11.11. Fax: (+32-2) 299.48.91
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.
http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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FOREWORD

This opinion is one in the series of opinions of the SCF on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Vitamin B_6 is a mixture of 6 inter-related forms pyridoxine (or pyridoxol), pyridoxal, pyridoxamine and their 5'-phosphates. Interconversion is possible between all forms (Bender, 1989). In this assessment the terms "vitamin B_6" and "pyridoxine" have been used interchangeably, with "pyridoxol" used when this particular form is discussed.

Pyridoxal phosphate plays an essential role in the metabolism of many aminoacids, and deficiency of this coenzyme can lead to many manifestations. Clinical signs include retarded growth, acrodynia, alopecia, skeletal changes and anaemia, while changes in neurotransmitters, such as dopamine, serotonin, norepinephrine (noradrenaline), tryptamine, tyramine, histamine, GABA and taurine, affect brain function and can lead to seizures and convulsions.

2. NUTRITIONAL BACKGROUND

The active form of the vitamin is pyridoxal phosphate, which is a coenzyme that is recognised as being required for the function of more than 60 enzymes involved with transamination, deamination, decarboxylation or desulfuration reactions.

Pyridoxine is present in food in the free form and as the glucoside. The glucoside may undergo partial hydrolysis in the gut lumen, or may be absorbed intact, following which it is largely excreted in the urine without hydrolysis (Gregory, 1990). Within cells pyridoxol and pyridoxamine are phosphorylated by a kinase enzyme and then oxidised to pyridoxal-5'-phosphate, which is the major intracellular form. All cells have the kinase but the liver is the major site for oxidation to pyridoxal phosphate; the liver is the main source of circulating pyridoxal, which is formed by the action of alkaline phosphatase on the hepatic pyridoxal phosphate (Merrill and Henderson, 1990). Excess pyridoxine is metabolised to 4-pyridoxic acid, which is eliminated primarily in the urine. The plasma concentrations of pyridoxal and its phosphate rise rapidly after a single oral dose of pyridoxol, followed by a rapid decrease in pyridoxal due to tissue uptake and phosphorylation. The acid metabolite is formed rapidly and

blood levels increase and then decrease to baseline levels within 12 hours (Speitling *et al.*, 1990).

Tryptophan metabolism is dependent on vitamin B_6 status, because the enzyme kynureninase, requires pyridoxal phosphate. This enzyme is especially sensitive to vitamin B_6 depletion. Loading doses of tryptophan are given to establish vitamin B_6 status (the tryptophan load test). Determination of the excretion of kynurenic and xanthurenic acids indicates vitamin B_6 nutritional status (Bender, 1989).

Vitamin B_6 is involved in the metabolism of sulphur-containing amino acids (methionine, taurine and cysteine (Sturman, 1986). The disease states homocystinuria and cystathioninuria are due to inborn errors of metabolism involving the enzymes cystathionine β-synthase (EC 4.2.1.22) and gamma-cystathionase (EC 4.4.1.1). Both diseases are characterised by wide ranging clinical signs and mental disturbances, and can be treated with large doses of pyridoxine, although some individuals are unresponsive to this treatment.

The majority of the body's vitamin B_6 is associated with the enzyme glycogen phosphorylase in muscle. When muscle glycogen reserves are depleted due to prolonged fasting, the vitamin is released from muscle, however, muscle pyridoxal phosphate is not released in response to a vitamin B_6 deficient diet, so that muscle reserves cannot be regarded as a storage form of the vitamin (Reports of the Scientific Committee for Food, 1993).

There are several studies that have examined pyridoxal phosphate plasma concentrations in relation to age. In 1964, Hamfelt reported that the plasma concentrations were lower in subjects greater than 60 years old, and the author speculated that this fall could be due to a nutritional defect, such as defective absorption, defective phosphorylation, or increased urinary excretion. Rose and co-workers (1976) also reported that plasma levels of pyridoxal phosphate decline with age. These results have been confirmed in women (Lee and Leklem, 1985), since middle-aged women (55 ± 4.0 years) had lower plasma pyridoxal phosphate and a higher urinary 4-pyridoxic acid than younger women (24.4 ± 3.2 years). Age-related changes in metabolism and tissue distribution of pyridoxine and its metabolite pyridoxal-5'-phosphate have been reported in rats (van den Berg *et al.*, 1990).

Lewis (1995) suggested that pyridoxine-related neurotoxicity (see later) may occur when the capacity of the liver to phosphorylate pyridoxine to the active pyridoxal phosphate is exceeded, and that the high circulating concentrations of pyridoxal give rise to the toxicity.

Daily requirements of vitamin B_6 have been determined and are affected by protein intake. Vitamin B_6 levels decline more rapidly in individuals with a high protein intake in comparison with those with a lower protein intake (Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy, 1991). In consequence, the daily requirement is related to protein intake rather than body weight; an intake of 15 μg/g dietary protein is recommended for adults, which is equivalent to about 2-3 mg per day (Reports of the Scientific Committee for Food, 1993). Since there are no storage facilities for vitamin B_6, a continuous daily intake is essential.

The Dietary and Nutritional Survey of British Adults (HMSO, 1990), which studied over 2000 people, reported that the majority of the intake by men was from food sources, whereas supplements represented a significant source (about 50% of total intake) for women more than 24 years old. The use of supplements by some women resulted in extremely wide inter-

subject variability and a skewed distribution with the highest 97.5th percentile intake being 16 mg/day in women aged 35-49 years.

Table 1. Pyridoxine intake in EU countries (mg/day).

	Population	n	Method	Supplements	Mean	97.5%
Austria[a]	individual	2488	24 h recall	?	1.68	3.43
Ireland[b]	men	662	7-day record	-	3.2	5.9
	women	717		-	2.4	4.1
	men	662		+	3.5	7.6
	women	717		+	3.6	30.3
Italy[c]	household	2734	7-day record	+	2.0	3.3
The Netherlands[d]	household	5958	2-day record	-	1.59	3.01
UK[e]	men	1087	7-day record	-	2.48	4.47
	women	1110		-	1.57	2.62
	men	1087		+	2.68	5.35
	women	1110		+	2.84	10.46

[a] Elmadfa *et al.* (1998) [b] IUNA (2000) [c] Turrini (INRAN)
[d] Hulshof and Kruizinga (1999) [e] HMSO (1990)

It has been suggested that individuals taking high-oestrogen contraception may have an additional requirement for vitamin B_6. Whilst there is some evidence that these oral contraceptives affect tryptophan metabolism, there is no evidence to suggest that they cause changes in vitamin B_6 status of the individuals (reviewed by Bender, 1987). In addition, there is no evidence that the combined oral contraceptive (oestrogen plus progestagen) affects the requirements for pyridoxine.

High doses of vitamin B_6 have also been used for the treatment of premenstrual syndrome, depression, Down's syndrome, hyperkinesis, autism, neurosis, Hodgkin's disease and Parkinson's disease (Sturman, 1986).

3. HAZARD IDENTIFICATION

The principal toxicity of concern associated with excessive intakes of vitamin B_6 is neuronal damage, and sensory and motor effects. The initial observations were from studies in experimental animals, but more recent studies in volunteers and patients, and case reports of patients have shown that the effects can be produced also in humans.

3.1. Neurotoxicity

3.1.1 Studies in animals

It has been known since 1940 that very large doses of pyridoxine (1-7 g/kg) in rats and dogs result in pronounced ataxia and weakness and degeneration of the spinal cord roots, posterior ganglia and peripheral nerves (Unna, 1940; Unna and Antopol, 1940a, b; Antopol and Tarlov, 1942). More recent studies have indicated species differences in the sensitivity to vitamin B_6 toxicity (Xu *et al.*, 1989), and have examined neuronal abnormalities in rats, guinea pigs and mice administered high doses of pyridoxine. Rats were administered 600-1200 mg/kg/day for 6-10 days, guinea pigs 1800 mg/kg/day for 10 days and mice 1800 mg/kg/day for 7 days or 1200 mg/kg/day for 6 weeks (as well as higher doses for shorter time periods). Neuropathy

with necrosis of sensory neurons in dorsal root ganglia, accompanied by axonal atrophy and breakdown of peripheral and central sensory axons, was observed in rats. Mice were resistant to such changes. Lower doses in rats (150-300 mg/kg/day) for up to 12 weeks also produced minor effects to the dorsal root ganglia and neuropathy with axonal atrophy and degeneration. The authors concluded that multiple factors including rate of administration, differential neuronal vulnerability and other factors influence species susceptibility.

There are limited data available on the underlying mechanism of toxicity of pyridoxine. Neuropathological changes in dogs have been correlated to changes in electrophysiological and functional tests at doses of 3 g per day (Schaeppi and Krinke, 1982). Two dogs were dosed until signs of morbidity appeared (after only 8 and 26 days), with ataxia and loss of reflexes observed in both dogs. The somatosensory maximum nerve conduction velocity was reduced. The neuropathological changes included lesions in the dorsal spinal column, dorsal spinal roots and ganglia, selected fibres in peripheral nerves and in the sensory spinal trigeminal roots. Nerve fibres located more deeply, and the spinocervical and spinocerebellular fibres were unaffected. Peripheral nerves showed signs of degeneration (demyelination, misformed Schwann cells, missing axons). Gross examination of the nervous systems of dogs treated with 150 mg pyridoxine/kg/day for 100-112 days, revealed abnormal opaque areas in the dorsal funiculus (Hoover and Carlton, 1981b). Histological examination showed degenerative lesions of varied severity in all dogs to which pyridoxine was administered. Lesions in the CNS were limited to the dorsal funiculus, the trigeminal nerves and the spinal tract of the trigeminal nerves. In these areas, the number of axons was reduced and the myelin was irregular and fragmented. The severity of the lesions in the rostal dorsal funiculi varied considerably among dogs from minimal to marked, with up to 70-80% of the nerves affected in some animals. The lesions were more severe in the rostal aspects of the dorsal funiculus than in the caudal. The lateral funiculi, the ventral funiculus and the gray matter of all segments were histologically normal.

Subtle effects on the central nervous systems, as measured by an attenuation of startle response, have been reported in rats fed diets containing between 7-2100 mg/kg of diet (equivalent to approximately 0.28-84 mg vitamin B_6/kg body weight/day) for 7 weeks (Schaeffer, 1993).

3.1.2. Studies in humans

The evidence for neurotoxicity in humans due to vitamin B_6 administration is largely related to a series of case reports of patients with severe effects associated with extremely high intakes. An important aspect of these cases is the duration of intake prior to the development of symptoms. Duration of intake is critical in the interpretation of the results of clinical trials that used vitamin B_6 for premenstrual syndrome (see later). Because both dose and duration of intake are important for B_6 neurotoxicity, the various case reports are described individually in the text and summarised in Table 2. The data (Table 2) indicate that cases of clinical neuropathy occur after about 12 months or longer treatment with doses of 2 g/day or less, whereas neuropathy can develop in less than 12 months at doses greater than 2 g/day.

Schaumburg *et al.* (1983) reported gradual progressive sensory ataxia and profound distal limb impairment in 7 adult patients following massive doses of vitamin B_6 (see Table 2). Unstable gait and numb feet were usually the first signs, and numbness and clumsiness of the hands followed. Profound distal limb impairment of position and vibration sense developed, while the senses of touch, temperature and pain were less affected. All tendon reflexes were

absent. The clinical profile was similar in all cases. The neurologic disability slowly improved once the patients stopped taking pyridoxine, and those examined after a prolonged period had made a satisfactory recovery. The transport of vitamin B_6 across the blood:brain barrier is saturable, and the authors speculated that the peripheral sensory neuropathy reflected the vulnerability of the neurons of the dorsal root ganglia because of the absence of the blood:brain barrier (which would protect neurons within the CNS from excessive circulating levels of the vitamin).

The single case reported by Berger and Schaumburg (1984) (Table 2) showed an improvement of her symptoms on stopping vitamin B_6 supplementation, and the authors attributed these symptoms to the administration of pyridoxine.

Table 2. Case reports of neuropathy in patients taking high doses of vitamin B_6.

Dose (g/day)	Duration (months)	Reference
0.1-0.2	36	Parry and Bredersen (1985)
0.1-2.5	9	Parry and Bredersen (1985)
0.1-4.0	72	Parry and Bredersen (1985)
0.2-0.5	24	Berger and Schaumburg (1984)
0.5	8	Parry and Bredersen (1985)
0.5	24	Parry and Bredersen (1985)
0.5-2.0	3	Parry and Bredersen (1985)
1.0	12	Waterson and Gilligan (1987)
1.0-2.0	36	Parry and Bredersen (1985)
1.5-2.0	24	Parry and Bredersen (1985)
1.5-2.5	>12	Parry and Bredersen (1985)
2.0	24	Friedman *et al*. (1986)
2.0	12	Parry and Bredersen (1985)
2.0	12	Parry and Bredersen (1985)
2.0	4	Schaumburg *et al*. (1983)
2.0	34	Schaumburg *et al*. (1983)
2.0	40	Schaumburg *et al*. (1983)
2.0-3.5	10	Parry and Bredersen (1985)
2.0-4.5	>12	Parry and Bredersen (1985)
2.0-5.0	2	Parry and Bredersen (1985)
2.0-5.0	4	Parry and Bredersen (1985)
3.0	4	Schaumburg *et al*. (1983)
3.5	1	Parry and Bredersen (1985)
4.0	10	Schaumburg *et al*. (1983)
5.0	2	Schaumburg *et al*. (1983)
6.0	3	Schaumburg *et al*. (1983)

Neuropathy associated with pyridoxine intake was described in 16 patients in another report (Parry and Bredersen, 1985 –see Table 2). All patients had symmetric distal sensory loss and the sensory nerve action potentials were absent or severely reduced in amplitude. Central peripheral degeneration confined to sensory axons strongly suggested that toxicity was directed against the dorsal root ganglia. Sural nerve biopsy in two patients showed that the myelinated fibre density was reduced and there was some myelin debris indicating axonal degeneration. The conditions of all patients improved after stopping vitamin B_6 treatment for between 3-18 months, but the symptoms were not fully resolved.

Waterston and Gilligan (1987) reported a case of a young woman who had been taking pyridoxine at a dose of 1000 mg/day for 12 months (Table 2), and whose symptoms resolved on cessation of pyridoxine intake.

Other studies have reported effects at higher doses. A mild motor neuropathy combined with a severe sensory neuropathy was reported in a patient who had taken 10 g/day for 5 years (Morra *et al.*, 1993). This case does not fit into the time-trend apparent in Table 2, and was not included because the time to the development of sensory effects was not reported. A case of by bilateral numbness after taking 2 g of vitamin B_6 daily for a period of 2 years (Friedman *et al.*, 1986 -see Table 2) improved within 32 weeks of cessation of B_6 intake.

A case-report of severe sensory neuropathy in a middle-aged man treated with 600 mg per day of pyridoxine for 8 months was not included in Table 2 because the subject was also receiving isoniazid (which also produces peripheral neuropathy) (Santoro *et al.*, 1991).

Neurological effects were detected when a 1 year old patient was treated with 1 g pyridoxine daily for hyperoxaluria, and these effects were reversed when the dose was reduced to 400 mg per day (de Zegher *et al.*, 1985).

3.2. Other adverse effects reported in humans and animals

Photosensitivity has been described as an adverse effect associated with pyridoxine intake. A 35 year old patient who had taken 200 mg pyridoxine per day as part of a multivitamin preparation showed erythema following exposure to UVA irradiation which the authors ascribed to the pyridoxine present in the multivitamin preparation (Morimoto *et al*., 1996). Skin lesions were reported in a woman who had taken massive doses (4 g/day) for a period of 4 years (Baer, 1984). Coleman *et al.* (1985) treated 400 patients with Down's syndrome with vitamin B_6 at pharmacological doses (35 mg/kg/day). Reported side effects included skin blisters that were related to sun exposure, vomiting and peripheral neuropathy; all patients who developed blisters did so after a minimum of four and a half years of treatment. Two patients developed motor and sensory polyneuropathy after 9 years administration of doses up to 50 mg/kg and their condition improved once vitamin B_6 administration had stopped.

The report of a high frequency of extrapyramidal dysfunction in a small group of patients with homocysteinuria, and who received pyridoxine, is difficult to interpret because of underlying differences between these patients and normal individuals (Ludolph *et al*., 1991).

Administration of doses of 100 or 500 mg B_6 per day for 10 days to a group of 58 medical students resulted in significantly impaired memorisation at 500 mg/day, and a non-significant decrease at 100 mg/day (Molimard *et al.*, 1980). This is a potentially important observation, given the dosage and the short duration of intake. The study was designed to investigate further an earlier unpublished observation of a decrease in "brain performance" from a double-blind study in medical students conducted in 1961. The study of Molimard *et al.* (1980) recruited 69 first year medical students who were randomly allocated to receive identical tablets of 50 mg or 250 mg pyridoxine or placebo to be taken twice per day for 10 days. Those who declared that they did not take the tablets were treated as a separate group. The subjects were given a simple digit coding test prior to treatment, immediately after treatment and 14 days later. In addition the subjects underwent a test on the medical physiology that had been taught during the treatment period, plus some simple numerical problems at the end of the treatment period. A total of 58 subjects completed all 3 digit coding

tests, which showed a highly significant improvement with time (a learning effect) in all groups. There were no significant differences in the uncorrected scores, but evidence of a dose-related decrease in the learning effect, with a highly significant difference between the placebo group and 500 mg/day group ($P<0.002$) but a smaller difference between the placebo and 100 mg/day group ($P<0.07$). There were no differences in the other tests of performance. In a second trial as part of the same publication, a group of 30 obese patients were randomly allocated to receive placebo or 20 mg or 1000 mg of pyridoxine per day for 15 days, with subjects given a number of tests before and immediately after treatment. An adverse dose-related effect was found for word recognition ($P<0.05$) but not for word or visual memorisation, together with a decrease in the results for a visual retention test in the pyridoxine treated group after treatment. These studies reported effects after short-term treatment, and no studies have investigated the relationship between dose and duration of treatment for such effects.

Many studies have described the effects of vitamin B_6 administration on spermatogenesis in animals (Mori *et al.*, 1989; 1992; Kaido *et al.*, 1991; Ide *et al.*, 1992). Administration of vitamin B_6 (125-1000 mg/kg/day) injected i.p. to rats for 6 weeks resulted in a decrease in the weight of the epididymides and the number of sperm was also decreased (Mori, *et al.*, 1989; 1992). Similar results have been reported by other workers (Kaido *et al.*, 1991; Ide *et al.*, 1992).

Daily oral doses of between 20-80 mg pyridoxine/kg to pregnant rats over days 6-15 of gestation produced no evidence of teratogenicity in the offspring (Khera, 1975). These doses of vitamin B_6 did not affect the number of implantations, corpora lutea or number of live pups. At higher doses (100-800 mg/kg), the number of implantations, live pups and corpora lutea in treated animals were increased in comparison with controls. However, doses of either 400 or 800 mg/kg significantly reduced the body weights of the pups.

4. DOSE-RESPONSE ASSESSMENT

Assessment of the dose-response relationship for pyridoxine-induced neurotoxicity is difficult because of the nature of the available data and potential inverse relationship between the duration of exposure and the doses that can be tolerated without adverse effects.

4.1. Studies in animals

Although pyridoxine is a water-soluble vitamin, which does not accumulate, the animal data indicate that there is a progressive development of the neurological lesion with time. The animal toxicity database on pyridoxine has been reviewed by Cohen and Bendich (1986) and was summarized by Munro (1997) in a paper presented to a symposium discussing the safety of vitamin B_6 (Shrimpton and Holmes, 1997). Krinke and Fitzgerald (1988) have shown that the type of neurotoxicity produced by pyridoxine in the rat is a function of the dose and duration of administration. Rats administered single high doses (1200 mg/kg) of pyridoxine were observed to have neuronopathy (damage to the cell body), those administered lower chronic doses (200 mg/kg for 12 weeks) were observed to have axonopathy to the distal portion of sensory nerves. These workers also reported that animals administered pyridoxine for 5 days a week had considerably less damage than those dosed every day.

There is an extensive toxicity database on the effects of vitamin B_6 in dogs, which supports both the clinical symptomatology in patients and the inverse relationship between duration

and dosage. Krinke *et al.* (1980) reported on the effects of the oral administration of pyridoxine (300 mg/kg/day for 78 days) on beagle dogs. Animals developed swaying gait within 4 to 9 days of start of treatment and severe ataxia between 8-30 days. Morphological examination on sacrifice, revealed widespread neuronal degeneration in the dorsal root ganglia and the Gasserian ganglia, degeneration of sensory nerve fibres in peripheral nerves, in dorsal columns of the spinal cord and in the descending spinal tract of the trigeminal nerve. Phillips *et al.* (1978) administered pyridoxine hydrochloride orally in gelatin capsules (0, 50 or 200 mg/kg/day) to 3 groups of female beagle dogs (4 in the control group, and 5 per treatment group) for 100-112 days. Four of the 5 animals in the high dose group (200 mg/kg/day) showed ataxia and loss of balance after 45 days of treatment, whilst the other animal showed clinical signs after 75 days: histological examination of tissues at termination showed bilateral loss of myelin and axons in the dorsal funiculi and loss of fibres in the dorsal roots. Animals in the low dose group (50 mg/kg/day) showed no clinical signs, but histological examination revealed loss of myelin in the dorsal nerve roots in all five dogs.
Hoover and Carlton (1981a) reported that all dogs (5 male and 5 female) treated with 150 mg pyridoxine/kg/day for 100-112 days developed neurologic disease characterised by ataxia involving predominantly the hind limbs at first, but with time, the fore limbs were also affected. Tests of postural reactions reflected proprioceptive abnormalities. Hind limb flexor reflexes were mildly reduced in two dogs and pain perception (pinprick) was mildly reduced in four. However, all dogs remained alert and cranial nerve and ophthalmologic tests were normal.

Comparison of the data of Phillips *et al.* (1978), Hoover and Carlton (1981a) and Krinke *et al.* (1980) indicates a possible inverse relationship between dose and time to effect.

4.2 Studies in humans

Interpretation of the data from investigations in humans and case reports (summarised above) indicate that adverse neurological effects are detected after very high doses (>500 mg/day which is equivalent to about 8 mg/kg/day). Because of the severity of the adverse effects, there have been few studies designed to define the dose-response relationship in humans. The most important clinical studies are summarised in Table 3 and discussed below.

4.2.1. Clinical studies that reported neurological effects

Berger *et al.* (1992) studied only extremely high doses, and did not define a non-effect level. Either 1 or 3 g of pyridoxine was given daily to 5 healthy volunteers until signs of either clinical or laboratory abnormality were present. Sensory symptoms and QST abnormalities were detected in all patients, and the subjects receiving the higher doses became symptomatic earlier than those receiving lower doses. The duration of treatments in the 5 subjects associated with the onset of symptoms was >14, 7, 4.5, 3.5 and 1.5 months in subjects receiving 12, 12, 19.6, 26.5 and 56.9 mg/kg/day respectively. The data demonstrated a clear inverse relationship between the dosage and the duration of consumption prior to the onset of symptoms.

Bernstein (1990) reviewed available data and concluded that women taking 500-5000 mg vitamin B_6/day as self-treatment for premenstrual tension have shown peripheral neuropathy within one to three years. The author stated that his own studies did not find neurological effects in 70 patients at doses of 100 or 150 mg/day for up to 5 years. However there is a discrepancy between this statement and the publications (Del Tredici *et al.* (1985) and

Bernstein and Lobitz (1988)) cited to support this conclusion, in relation to the numbers of patients, the dosage (150-300 mg/day) and most importantly the duration (mostly less than 6 months). Bernstein (1990) hypothesised that there may be predisposing factors which may make some individuals more sensitive.

The development of peripheral neuropathy has been reported in patients taking lower doses. A short report (Dalton, 1985) stated that 40% of women who had been taking vitamin supplements for premenstrual tension and who had plasma vitamin B_6 levels above normal (3-18 ng/ml), developed various clinical signs consistent with peripheral neuropathy. The signs included shooting and tingling pains, paraesthesia of limbs, clumsiness, ataxia or peri-oral numbness. The vitamin B_6 intake of these women ranged from 50-300 mg per day and involved a variety of multivitamin preparations. Two months after stopping all supplements, 27 of the women were reassessed and all showed improvement.

In a subsequent study (Dalton and Dalton, 1987), vitamin B_6 intake and clinical signs were monitored in women attending a private clinic specialising in the treatment of premenstrual tension. Of 172 women who were found to have elevated vitamin B_6 serum levels (>18 ng/ml), 103 (60%) complained of neurological symptoms, while the other 69 had no symptoms. The neurological symptoms included paraesthesia, bone pains, hyperaesthesia, muscle weakness, fasciculation and numbness. Symptoms were symmetrical. The daily dosages in both groups ranged from <50 mg to >500 mg and the average daily dose was 117 ± 92 mg in the group described by the authors as the "neurotoxic" group and 116 ± 66 in the "controls". Those complaining of the symptoms had been taking the supplement for 2.9 ± 1.9 years, while those who had no symptoms had a duration of intake of 1.6 ± 2.1 years ($P<0.01$). Three months after stopping vitamin B_6 intake, 55% of the women reported partial or complete recovery from the neurological symptoms and at 6 months, all reported complete recovery and the areas of hyperaesthesia and numbness noted at the initial examination had disappeared. Seven women who had inadvertently not stopped vitamin B_6 intake all reported a continuation of their symptoms. Three women had subnormal serum B_6 levels on cessation of supplement intake, and restarted B_6 at a daily dose of 50 mg; however, symptoms returned and they stopped the supplement intake. In one case, a woman who had taken 75 mg of B_6 daily together with multivitamins, zinc and magnesium, for 2 years, and had serum B_6 level of >34 ng/ml, complained of paraesthesia of the hands, electric shock pains in her head, numbness of the finger tips and itching between her shoulder blades. Examination revealed patchy areas of hypersensitivity on her back and lower limbs, especially her shins. On stopping vitamin B_6 treatment, all symptoms eased within 3 months. However, on restarting B_6 intake at 50 mg per day for 3 months, the same neurological symptoms returned. The appearance of neurological symptoms at lower doses appears to be related to duration of intake which is compatible with the conclusion from Table 1. This study has been severely criticised because of its design; all subjects received vitamin B_6 and the comparisons were between those who did, and those who did not report adverse effects. The adverse effects may have predated treatment with B_6. The only evidence for cause and effect relates to the consequence of stopping or not stopping intake, and correlations with duration of intake. Individuals, who had reported adverse effects, had been taking B_6 for longer than those who did not have symptoms, and a higher proportion (70% compared with 55%) had serum B_6 levels >34 ng/ml.

Table 3. Clinical studies on pyridoxine in relation to neurological effects (see Table 2 for individual/anecdotal evidence)

Authors	Subjects	Number	Dosage (mg/day)	Duration of treatment	Findings	Conclusions
Baker and Frank (1984)	Elderly	6	225	up to 1 year	Adverse effects not reported	Too few subjects to provide useful data; full data not published
Berger *et al* (1992)	Adults	5	1000-3000	up to 7 months	All subjects developed abnormal measurements of vibration and/or thermal thresholds; 4 subjects developed clinical symptoms	Clear evidence of adverse effects at high doses with an inverse relationship between dose and symptom-free duration
Bernstein and Lobitz (1988)	Diabetic patients with pre-existing neuropathies	16	150	up to 6 months	No changes in motor conduction velocity at 5 months	Limited duration and high drop-out rate (only 5 subjects studied at 5 months)
Bonke and Nickel (1989)	Men (marksmen)	18	60 (n = 8) 600 (n = 10)	8 weeks	Shooting performance (a reflection of tremor); significant improvement in score over the 8 week period compared to placebo	Duration too short to assess neurological effects
Brush (1988)	Patients with premenstrual syndrome	cohort 1 = 630	40-200	mostly less than 1 year; 76 for 1-5 years	No neurological effects reported	Only 7% of patients were treated for 3 or more years. 140 subjects received >100 mg per day but their duration of treatment is not defined
Brush *et al* (1988)	Patients with premenstrual syndrome	cohort 2 = 336	40-200	duration not stated	6 subjects reported mild tingling/ numbness described as "definite side-effects"	No details given about duration of treatment
Dalton (1985)	Patients with premenstrual syndrome	58	50-500	Not defined	Significant reductions in symptoms such as headache tiredness and "neuropathy" 2 months after stopping B_6	Insufficient details to assess data; no control group data
Dalton and Dalton (1987)	Patients with premenstrual syndrome	172	<50-<500	<6 months->5 years	Patients with neurological symptoms had similar daily intakes but greater duration (2.9 years); reversal of symptoms on cessation of intake	A selected group of patients with high serum B_6 which showed a high incidence of "neurological" symptoms. There was no control group and the evidence of causality is the relationship with duration of intake and reversibility

(Cont.)

Table 3 (Cont.). Clinical studies on pyridoxine in relation to neurological effects (see Table 2 for individual/anecdotal evidence)

Day (1979)	Patients with premenstrual syndrome	67	100	1 month	No assessment of side effects	Duration too short to assess neurological effects
Del Tredici *et al.* (1985)	Patients with carpal tunnel syndrome	24	150 or 300	4 months	No changes in distal motor latency or self-assessment questionnaire	Duration too short to assess neurological effects
Ellis *et al* (1979) (and studies cited); Ellis (1987)	Patients with carpal tunnel syndrome	35	100-300	up to 12 weeks	No adverse neurological effects reported	The condition may be due to pyridoxine deficiency; typical treatment schedule of 12 weeks (Ellis, 1987) is of too short duration to access neurological effects
Kerr (1977)	Patients with premenstrual syndrome	70	40-100	2 months	No assessment of side effects	Duration too short to assess neurological effects
Mitwalli *et al* (1984)	Patients with hyperoxaluria (kidney stones)	22	250-500	1-6 years	No neurological complications in 22 patients or nerve conduction abnormalities in 7 patients studied in detail	Small group size but very extended duration; influence of the disease on pyridoxine handling, requirements and neurological response are not known
Mpofu *et al* (1991)	Patients with homocysteinuria	17	200-500	10-24 years	No abnormalities of motor or sensory nerve conduction velocities	Small group size but very extended duration; the absence of effects at doses equivalent to 10-90 mg/kg/day suggests that these patients may show reduced responsiveness to the neuronal adverse effects of pyridoxine
Pauling (1984) cites Hawkins	Undefined patients	>5000	200	not given	No details	No details available; cannot be assessed
Pullon *et al* (1989)	Women	410	not described	not described	No assessments of possible neuropathy	Results from a survey of 1826 women; no data on tolerability and side effects
Tolis *et al* (1977)	Women	9	200 or 400	2 months	No effects on growth hormone or prolactin	Small number of subjects and very limited duration of treatment; no assessment of neurological effects
Williams *et al* (1985)	Women with premenstrual syndrome	204 (out of 434)	100	3 months	No difference in side effects between treatments and placebo groups	Duration too short to access neurological effects
Wyatt *et al* (1999)	Women with premenstrual syndrome	526 (out of 910)	50-600	up to 4 months	Data assessment for reports of side effects; 1 reported case of neurological side effects	A systematic review of published and unpublished randomised placebo controlled trials; all studies of inadequate duration

Brush (1988) reported retrospective data on a group of 630 women with premenstrual syndrome who were treated with pyridoxine either alone or in combination with other medications. This cohort appears to have been the same as that described by Brush *et al.* (1988), and mentioned by Brush and Perry (1985) in their letter concerning the Dalton study.

Neuropathy was not reported in the group of 630 women who received between 80 and 200 mg pyridoxine daily for premenstrual syndrome (Brush, 1988; Brush and Perry, 1985). This same cohort of patients was described by Brush *et al*. (1988), and it is clear that the data are limited by the duration of the study because 80% of the subjects were treated for 12 months or less, and 93% for 24 months or less: neurological assessment was not performed and the tolerability of the treatment was assessed by the patients. Although the authors state that there were no adverse effects in the 1976-1983 cohort of 630 patients, Brush (1988) tabulated "definite side-effects" with 5 cases of dizziness and 6 cases of mild tingling in the 1983-1986 cohort of 336 patients; the authors ascribed this to the higher dose (200 mg/day) in this cohort and/or the adverse publicity at the time.

4.2.2. Clinical studies that did not report neurological effects

In contrast to the "positive" studies described above, there are a number of publications that did not find evidence of adverse effects in humans receiving high doses of vitamin B_6. Interpretation of the various studies is complicated by differences in the duration of treatment. A large number of the studies are in women taking high doses of vitamin B_6 for premenstrual syndrome. The various "negative" studies are described below, followed by a summary of the dose, duration and outcome for both positive and negative studies.

No adverse effects were reported in a small study by Bonke and Nickel (1989) in which small numbers of healthy volunteer marksmen were given a mixture of vitamin B_1 (90 or 300 mg), B_6 (60 or 600 mg) and B_{12} (120 or 600 μg) daily for a period of 8 weeks; however, there was an increase in shooting accuracy, indicating a reduction in tremor, at both doses. Adverse effects were not reported in a group of 6 elderly individuals given 225 mg pyridoxine per day for one year (Baker and Frank, 1984). In a letter to the New England Journal of Medicine, Pauling (1984) stated that a similar dose (200 mg pyridoxine daily) had been given to more than 5000 subjects without reports of side-effects (but these data cannot be evaluated because the duration of intake is not known and the cited reference (Hawkins, 1973) is not available in peer-reviewed literature).

A cohort of 434 patients with premenstrual syndrome was divided into two groups: one group received 100 mg pyridoxine per day and the other group were given a placebo. The patients were allowed to increase the dose to 200 mg/day if they considered they were receiving no benefit from the initial treatment (Williams *et al.*, 1985). Patients were studied over 3 menstrual cycles only and therefore the duration of intake and dose were inadequate to allow assessment of any possible neurotoxicity associated with pyridoxine.

Two preliminary reports (Kerr, 1977; Day, 1979) studied the potential value of pyridoxine in the treatment of premenstrual syndrome. Neither study was of sufficient duration (2 months and 7 months respectively) or assessed symptoms sufficiently rigorously to be of value in relation to establishing possible adverse effects of vitamin B_6. A large group of women with premenstrual symptoms (n = 1826) was studied by Pullon *et al.* (1989) largely in relation to the syndrome and its management, but this large study provided no data on possible pyridoxine neuropathy. A recent systematic review of studies on the use of vitamin B_6 in

premenstural syndrome (Wyatt *et al.*, 1999) showed an improvement compared to placebo. The review considered 9 published studies that involved 940 women. Adverse effects were limited to one case of neuropathy that could be attributed to pyridoxine. Dosages ranged from 50-600 mg/day, but the studies were too short in duration (usually 2-4 months) to exclude the possibility of neuropathy after prolonged intake at such intakes.

A small study in patients with carpal tunnel syndrome by Del Tredici *et al.* (1985) described the treatment of 16 patients with 150 mg vitamin B_6 for 4 months and 8 patients with 300 mg B_6 for 4 months. Measurement of distal motor latency indicated a clinical improvement. No details of neurological assessment were given and the duration of the study limits its value for assessing adverse effects after long-term treatment. Ellis *et al.* (1979) reported detailed results on one patient out of a group of 22 patients with carpal tunnel syndrome who had been treated with pyridoxine (120 mg/day). Treatment with either 2 mg or 100 mg per day resulted in clinical improvement in symptoms ($P<0.01$ and $P<0.001$ respectively), which is consistent with the authors proposal that this condition is related to pyridoxine deficiency. A subsequent paper, Ellis (1987) described the successful treatment of 35 selected cases of carpal tunnel syndrome with pyridoxine (100-200 mg per day), which took 12 weeks to improve or relieve the signs and symptoms.

No clinically significant side effects were reported in a group of ten 6-year old patients with autism who were given a combination of pyridoxine (639 mg) and magnesium (216 mg) daily for a period of 10 weeks using a double blind, placebo-controlled study design (Findling *et al.*, 1997).

Additional data have been published from studies in patients with known metabolic abnormalities or inborn errors of metabolism. These are given briefly below for completeness, but their interpretation in relation to the safety of vitamin B_6 for normal subjects is unclear.

Bernstein and Lobitz (1988) reported no deterioration of peripheral nerve function in a group of 16 patients with painful diabetic neuropathy who were treated with pyridoxine 150 mg/day for a period of up to 6 months, but only 4 subjects completed the study for the full 6 months.

Mitwalli *et al.* (1984) reported the absence of neurological effects in a group of 22 patients with hyperoxaluria who developed kidney stones, and who received doses of 250-500 mg of pyridoxine per day for 8 months to 6 years (average 2.3 years). Nerve conduction studies in a sub-group of 7 of these patients revealed no abnormalities. This paper is frequently stated as supporting the safety of intermediate doses of pyridoxine but it is limited by the study size; also hyperoxaluria can be a result of pyridoxine deficiency (Nath *et al.*, 1990), so that a metabolic abnormality related to pyridoxine cannot be excluded.

Patients with homocysteinuria may be given high dose pyridoxine treatment for many years from birth. A brief report by Mpofu *et al.* (1991) described a group of 17 subjects who were given 200-500 mg of pyridoxine per day for between 7 and 24 years. Because the patients were treated from ages 2 weeks to 14 years, the doses ranged from 10-90 mg/kg/day during the first 10 years of life. The treatment was associated with very high concentrations of pyridoxine and pyridoxal phosphate in the plasma. Nerve conduction was within the normal range in each of the 4 nerves studied in each patient. Although this study appears to support the safety of doses of 200-500 mg of pyridoxine per day, such patients typically show a range of mental, ocular, skeletal and cardiovascular disease if untreated. The influence of the condition on the response to potentially neurotoxic doses of pyridoxine is not known, but the

absence of effects at such high doses (comparable to those of Berger *et al.,* 1992) raises questions over the usefulness of such data in relation to the general population.

4.3. Establishment of a no-observed adverse effect level (NOAEL)

The available dose-response data in humans are difficult to analyse because many of the publications relate to case reports and true incidence data are not available. The studies of Schaumburg *et al.* (1983) showed the potential severity of the hazard but there was little information on dose-response. Parry and Bredesen (1985) reported a case series of 16 patients with sensory central-peripheral distal axonopathy, who had taken from 0.2 to 5 g/day for prolonged periods. Berger *et al.* (1992) reported adverse effects in 4 out of 5 healthy volunteers who were given 1 g or 3 g/day in a controlled study. Berger and Schaumburg (1984) described a case of reversible pyridoxine-induced, sensory ataxia in a woman who had taken 200 mg/day for 2 years followed by 500 mg/day for 1 year. A similar case was reported by Waterston and Gilligan (1987) in a woman who had taken 1000 mg/day for 1 year.

The data described above, and summarised in Table 2, are the basis for the generally accepted conclusion that 500 mg of pyridoxine daily represents a potentially toxic dose for adults.

The data for doses between 100 mg/day and 500 mg/day are less clear, largely because they relate to case reports or observations in groups of patients, that were not subject to a proper double-blind, placebo-controlled evaluation. The case series described by Parry and Bredesen (1985) included 3 patients who had taken <1 g/day, all of whom had taken the high dose supplements for more than 1 year; one subject had taken a maximum of 200 mg/day for at least 3 years. Brush (1988) reported a low incidence of possible pyridoxine related side-effects (5 subjects reported tingling and/or numbness) in a cohort of 336 subjects who had taken 200 mg per day (see above); however the duration of treatment and details of other medication for these subjects were not given. Similar effects were not reported in a previous group, but the majority had been followed for less than 12 months (Brush, 1988).

As discussed above, many of the observational clinical studies which report no adverse effects of pyridoxine are limited in relation to duration of intake, size of study group, lack of adequate assessment of adverse effects and/or lack of an appropriate protocol (double-blind, placebo-controlled) (see Wyatt *et al.*, 1999). Many of these criticisms can also be applied to the study of Dalton and Dalton (1987) with the important exception of the duration of exposure. This study divided a group of 172 women into those who reported altered sensations in their limbs or skin, or muscle weakness, or pain (n = 103), and those who did not. Comparison between the two sub-groups was used as the basis for the analysis, which found no difference in pyridoxine intake, but a significantly greater duration of intake in those with symptoms (2.9 years) compared with those without (1.6 years). Although this study is open to criticism, the finding in relation to duration is not inconsistent with other data at higher doses and in animals. The authors did not give a separate statistical analysis in relation to the difference in duration of intake for those who reported likely pyridoxine-related symptoms such as paraesthesia (n = 59), hyperaesthesia (n = 33) and numbness (n = 21) compared to the symptom-free group.

The lower end of the dose-response for pyridoxine-related neurological effects has not been defined clearly, especially for long-term intake. The various studies show clear effects at 500 mg/day or more, a low incidence of effects at 200 mg/day in one study (if taken for up to 2 years) and the possibility of effects at about 100 mg/day (if consumed for about 3 years). In

consequence a clear NOAEL has not been established and an intake of 100 mg/day cannot be excluded as a possible effect level for long-term intake.

4.3.1. Previous reviews and evaluations

There have been a number of reviews published on the establishment of a safe upper limit for pyridoxine. Bender (1989) reviewed the risks and benefits of B_6 therapy and concluded that doses of "50 mg/day" and above must be considered to be potentially hazardous. Although Bendich and Cohen (1990) in their review of published data concluded that total amounts of 100 g taken over periods of 20 months (which can be estimated as equivalent to approximately 170 mg/day) are not associated with neuropathy, the database they presented included 2 cases in which neuropathy was reported at doses of around 100 mg/day for approximately 14 months. An earlier SCF evaluation (1993) concluded that "intakes greater than 500 mg/day are associated with neurological damage and intakes of more than 50 mg/day are potentially harmful in adults". An upper level of 10 mg per day was suggested by the UK Committee on Toxicity in 1997, which was based largely on the data from studies in dogs, divided by a safety factor, and supported by the data from the study of Dalton and Dalton (1987) and other available human data.

The Food and Nutrition Board of the Institute of Medicine (FNB, 1998) in the USA recently set an upper level of 100 mg/day for adults. That report did not use the study of Dalton and Dalton (1987) to establish the NOAEL because they considered that the weaknesses of the study and the inconsistency of the results with the weight of evidence pertaining to the safety of higher doses of pyridoxine ruled out the use of these data to base an upper level. The report highlighted a number of methodological weaknesses in the study, but in reality many of these apply also to the other studies available on pyridoxine. The FNB report identified a NOAEL of 200 mg/day based on two studies (Bernstein and Lobitz, 1988; Del Tredici *et al*., 1985). The FNB report (FNB, 1998) supported the NOAEL of 200 mg/day with additional studies that they stated were not as carefully executed or reported as the study by Bernstein and Lobitz (1988), but which reported no neuropathy in hundreds of individuals given pyridoxine doses of 100 to 500 mg/day (Brush *et al*., 1988; Ellis *et al*., 1979; Mitwalli *et al*., 1984; Tolis *et al*., 1977). Careful scrutiny of the papers used by the FNB to establish a NOAEL of 200 mg/day shows that the studies that were the principal basis were of too short duration to be useful; Bernstein and Lobitz (1988) reported data for only 16 patients, at doses of 150 mg/day and the duration of intake was only up to 6 months (with only 5 subjects studied after 5 months), while Del Tredici *et al*. (1985) studied only 24 patients for 4 months. The large number of subjects studied in the other publications used to support the NOAEL of 200 mg/day was largely due to the work of Brush and colleagues (which was not unequivocally without possible adverse effects – see above), whereas Ellis *et al*. (1979) reported on only 22 subjects [Ellis (1987) discusses data for 35 cases], Mitwalli *et al*. (1984) gave data for only 7 in detail (but these had been treated for 2.8 years) and Tolis *et al*. (1977) only 9 patients. Against this general background of inadequate data, especially with respect to the duration of treatment, it is not reasonable to dismiss the study by Dalton and Dalton (1987).

These previous analyses did not consider adequately the possibility of an inverse relationship between duration of intake and the lowest dose producing adverse effects. Also, these reviews did not consider intakes during potentially critical periods of development.

5. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The toxicity of concern with pyridoxine is neurotoxicity, which has been demonstrated clearly in experimental animals and humans. Other effects reported in animals, which occur at high doses (see earlier), have not been investigated in humans, because the main effect in animals is on spermatogenesis and the main use of high doses in humans is for premenstrual tension.

The deficiencies and uncertainties in the available database make the identification of a clear no-effect intake very difficult. Daily doses of about 500 mg are necessary to produce severe neurological effects. In contrast, some of the subjects who reported minor neurological symptoms in the study of Dalton and Dalton (1987) were taking only 50 mg of pyridoxine per day. The dose-response data in humans, which are the basis for determining the upper level, are derived largely for women with premenstrual syndrome. Pyridoxine neuropathy develops very slowly in humans even at high doses; intake for 12 months or longer is necessary to produce neurotoxicity at doses of 2 g per day or less (see Table 2). Severe effects have been reported in a number of case reports that involved daily intakes about 500 mg, with one case report after 100-200 mg for 36 months (Table 2). The second cohort described in the paper by Brush (1988) is consistent with mild effects at 200 mg/day in a small number of treated patients. The data in the study of Dalton and Dalton (1987), and their validity are critical to establishing the upper level. The study of Dalton and Dalton (1987) is difficult to interpret with respect to both the incidence and also the dose-response relationship; however, the duration difference and the reversibility data indicate that the effects cannot be dismissed. Based on the apparent inverse relationship between dosage and duration of intake, a significant difference in duration of intake (average 2.9 years), but not dosage in women with "neurological effects" while taking low doses is exactly the relationship that would be predicted.

In summary therefore the data indicate that severe toxicity can be produced at doses of 500 mg/day or more, and that minor neurological symptoms may be apparent at doses of 100 mg/day or more if consumed for long periods. Neurotoxicity has not been reported at doses of 100 mg/day when consumed for a period of up to a few months but such data are not relevant to assessment of neurotoxicity, because of the slow development of symptoms at high doses and the inverse relationship between dosage and the onset of symptoms.

An upper level has been calculated by dividing the average intakes in the study of Dalton and Dalton (1987) of approximately 100 mg per day (the mean intake was 117 mg/day and the median was <100 mg/day) by a factor of 2, because the intake corresponds to a possible effect level for long-term intake, and by a second factor of 2 to allow for deficiencies in the database. A larger uncertainty factor is considered not to be necessary, because the data of Dalton and Dalton (1987) were for a sub-group with high plasma concentrations, and because the resulting upper level of 25 mg per day has not been associated with adverse effects in any of the large number of published studies. This value is below the lowest doses associated with minor neurological effects following long-term intake, and is 10- or 20-fold lower than doses associated with more severe adverse effects. In addition an intake of 25 mg/day is below the doses producing subtle and minor effects when taken for only 10 days (Molimard *et al.*, 1980).

There are no subgroups that are known to be unusually susceptible to the adverse effects of vitamin B_6. There are no reports of adverse neurological effects on infants born to mothers with high intakes of vitamin B_6, or of neurological effects in lactating women, although

controlled clinical studies are lacking. Therefore the UL of 25 mg per day should be considered to apply also to pregnant and lactating women. However, there are no adequate animal developmental neurotoxicity data that address these stages of development, and this is identified as a database deficiency (see recommendations).

The upper level intakes for children are based on body weight differences compared to adults:

Age (years)	Tolerable Upper Intake Level (UL) (mg per day)
1-3	5
4-6	7
7-10	10
11-14	15
15-17	20
Adults	25

6. CHARACTERISATION OF RISK

There is a wide margin between the UL of 25 mg per day and intakes from food sources only (see Table 1) and there are no safety concerns in relation to vitamin B6 intake from food sources. The combined intake that would occur from the foods and from supplements is generally below the UL. However, recent data on vitamin B_6 intake from foods and supplements in Ireland indicate that, while the 95th percentile intake of 18-64 year old women is 8 mg/day, the intakes of 2.5% of this population group exceed the UL of 25 mg (range of intake of 30-62 mg/d) due to supplement use (IUNA, 2000). There are supplements available in some countries that contain amounts per tablet/capsule that are considerably higher than the upper level. The UL does not apply to individuals taking vitamin B6 under medical supervision.

7. RECOMMENDATIONS

Neurotoxicity has been reported only after prolonged periods of treatment at high doses. The vitamin itself is rapidly eliminated and there is no molecular mechanism to explain the delay between exposure and the development of adverse effects. Information on the mechanism may allow a better understanding of the inter-relationships of the dosage, the duration of intake and the severity of effect.

Pyridoxine deficiency has a significant effect on neuronal development (Kirksey *et al.*, 1990), but there are no data on the neuronal toxicity of excessive pyridoxine during development of the nervous system. A major deficit in the database for this vitamin is the absence of information from adequate developmental neurotoxicity studies. Such research would clarify if the dose-response relationship of the developing nervous system is comparable to that indicated by studies in adults. Information on the neurobehavioural development of the offspring of women who become pregnant while taking high-doses of vitamin B_6 for pre-menstrual syndrome, or who were intentionally given high doses of B_6 during pregnancy (see Ellis, 1987), may provide data relevant to this issue.

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