

Risk Assessment

Vitamin B₆ (Pyridoxine)

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General Information

Chemistry

Pyridoxine is a water-soluble vitamin. Pyridoxine is composed of three forms (vitamers), pyridoxine, pyridoxal and pyridoxamine, all of which are normally present in foods. Pyridoxine hydrochloride is photosensitive and will degrade slowly when exposed to light.

Natural occurrence

Pyridoxamine and pyridoxal are found in animal products, and pyridoxine in animals and plants.

Occurrence in food, food supplements and medicines

Pyridoxine is found in chicken (4.2 mg/kg), fish, liver, kidney, pork, eggs (1.1 mg/kg), milk, wheatgerm (11.5 mg/kg) and brewer's yeast (25 mg/kg). Other sources include brown rice (5.5 mg/kg), soybeans (6.3 mg/kg), oats, whole-wheat grains, peanuts and walnuts (7.3 mg/kg). Long-term storage, canning, roasting or stewing of meat and food processing techniques can destroy pyridoxine. Boiling reduces the pyridoxine content of food because of losses into the water. Pyridoxine is present in a number of food supplements generally at doses up to 10 mg/day but some single dose food supplements may contain 50 to 150 mg. Single nutrient products (recommended maximum daily doses of 10 – 100 mg) are available without the supervision of a pharmacist.

As a licensed medicine, pyridoxine hydrochloride is also present in various multivitamin preparations for the prevention and treatment of vitamin deficiencies (maximum daily doses of 0.5 – 30 mg). Products containing pyridoxine (maximum daily dose of 10 mg) combined with other constituents are available from a pharmacist.

Recommended amounts

Recommended intakes of pyridoxine are based on protein intake. In the UK, the RNI is set at 15 µg/g protein for adults. This is equivalent to approximately 1.4 and 1.2 mg/day in the UK for males and females respectively. In the US, the Recommended Daily Allowance is set at 1.3 mg/day, and it is approximately 1.6 mg/day in Australia. Pregnant and lactating women and older people, who have low vitamin B₆ levels, can usually increase their intake through a high-protein diet.

Analysis of tissue levels and pyridoxine status

Pyridoxal phosphate has been determined enzymatically using tyrosine apodecarboxylase or by fluorimetric methods. The preferred method is high-pressure liquid chromatography. Vitamin B₆ status has also been assessed using erythrocyte aminotransferases and the tryptophan loading test; the latter is not a reliable indicator of vitamin B₆ status in persons receiving oestrogens or with increased secretion of glucocorticoids.

Brief overview of non-nutritional beneficial effects

Pyridoxine is an approved treatment for sideroblastic anaemias and pyridoxine-dependent errors of metabolism. Pyridoxine has also been claimed to alleviate the symptoms of a range of conditions including premenstrual syndrome, sickness during pregnancy, carpal tunnel syndrome, hyperhomocystinaemia (a risk factor for cardiovascular disease) and neuropathies.

Function

The cofactor forms of pyridoxine are pyridoxal-5'-phosphate and pyridoxamine-5'-phosphate. Pyridoxal phosphate is involved as a cofactor particularly in the metabolic transformation of amino acids, including decarboxylation, transamination and racemisation.

Vitamin B₆ is a cofactor in the conversion of tryptophan to 5-hydroxytryptamine and of methionine to cysteine. Pyridoxine can modify the action of steroid hormones *in vivo* by interacting with steroid-receptor complexes. Pyridoxine is essential for the manufacture of prostaglandins and for the formation of red blood cells.

Pyridoxine is involved in cellular replication and antibody production. An adequate supply of pyridoxine is necessary for the function of the nervous system. The vitamin is involved in the biosynthesis of several neurotransmitters, including serotonin, gamma amino-butyric acid (GABA), dopamine and noradrenaline and so has a role in the regulation of mental processes and mood. It is also involved in sodium-potassium balance, histamine metabolism, the conversion of tryptophan to niacin, absorption of vitamin B₁₂ and the production of hydrochloric acid in the gastrointestinal tract.

Deficiency

Pyridoxine deficiency is unusual in humans. Children who had been given milk in which the pyridoxine had been destroyed by overheating, displayed various symptoms, including weakness, irritability, nervousness, susceptibility to noise, weight loss and insomnia. Adult volunteers on a pyridoxine deficient diet became depressed and irritable, with 'a loss of sense of responsibility'. They also experienced a greasy rash on the forehead and around the nose and cracking of the lips and tongue.

Pyridoxine dependency is a rare autosomal recessive disorder in which the enzyme glutamate decarboxylase, which is involved in the synthesis of GABA, has a defective binding site for pyridoxal phosphate. Much higher tissue levels of pyridoxal phosphate are necessary for the enzyme to have any significant activity. The condition results in seizures of prenatal or neonatal onset and treatment with large doses of pyridoxine is necessary to prevent severe mental retardation or death.

It has also been suggested that pyridoxine deficiency may be a factor in hyperhomocysteinaemia, which is associated with an increased risk of cardiovascular disease.

Pyridoxine deficiency has also been reported to be associated with immune dysfunction, kidney stones, cancer and carpal tunnel syndrome, although the evidence for these links is variable.

Interactions

Pyridoxine requires riboflavin, zinc and magnesium to fulfil its physiological function in humans. Pyridoxine supplements reduce the therapeutic effect of levodopa, a naturally occurring amino acid used to treat Parkinson's disease. Pyridoxine also interacts with other drugs such as isoniazid, phenytoin, theophylline and phenobarbitone. It has been claimed that women taking oral contraceptives may have an increased requirement for pyridoxine.

Absorption and bioavailability

The phosphate forms of vitamin B₆ in food are dephosphorylated in the intestinal lumen, and pyridoxine, pyridoxal and pyridoxamine are taken up from the small intestine by an energy-dependent process. All three are converted to pyridoxal phosphate in the tissues.

A proportion of the vitamin B₆ present in plant-based foods is biologically unavailable because it is present as pyridoxine glycosides that are not hydrolysed by intestinal enzymes. These glycosides may be absorbed, but do not act as a coenzyme in the body and are excreted unchanged in the urine.

All three forms of vitamin B₆ (pyridoxine, pyridoxal and pyridoxamine) are readily absorbed in the small intestine. The extent of absorption is decreased following gastric resection or in patients with malabsorption syndrome. Excess pyridoxine is excreted in the urine, and an adequate daily intake is therefore essential.

Distribution and metabolism

Pyridoxine in food is converted to active forms in the liver, a process which requires zinc and riboflavin.

Vitamin B₆ is stored in the liver, with about 50% also being present in muscle, bound to glycogen phosphorylase. Pyridoxine is also stored in the brain. The total body storage for adults is between 6 and 27 mg. Pyridoxine in the form of pyridoxal crosses the placenta, with foetal plasma concentrations being five times the level found in maternal plasma. The three forms of vitamin B₆ are present in body tissues, mainly as 5-phosphorylated derivatives of pyridoxal and pyridoxamine. The half-life of pyridoxine is 15-20 days, and it is not significantly bound to plasma proteins.

Pyridoxine, pyridoxal and pyridoxamine are all largely metabolised in the liver through phosphorylation by pyridoxal kinase. Pyridoxine phosphate is oxidised to the active coenzyme form, pyridoxal-5-phosphate, by an enzyme found mainly in liver. Pyridoxal-5-phosphate interconverts with pyridoxamine-5-phosphate through enzymatic transamination. The phosphorylated forms are hydrolysed by phosphatases.

Pyridoxal is oxidised in the liver to pyridoxic acid.

Excretion

Pyridoxic acid, the main excretory metabolite, is eliminated via the urine.

Toxicity

Human data

Long-term use of pyridoxine (generally in excess of 200 mg/day) has been reported to result in paraesthesiae, somnolence and low serum folic acid levels. Large doses of pyridoxine (usually quoted as over 2000 mg/day) can cause nerve damage. Symptoms include tingling in the hands and feet (paraesthesiae), a stumbling gait, perioral numbness, a characteristic 'stocking-glove' sensory loss and lack of muscle coordination. Duration of pyridoxine use is important as well as dosage, with lower doses of pyridoxine (500 mg/day or less) consumed for many months or years also being associated with neuropathy. In most, but not all reported cases the damage has been generally reversible. Night restlessness, vivid dreams, sun sensitivity and an acne-like rash may also occur with high doses (150 mg/day or more) of pyridoxine.

Supplementation trials

A number of pyridoxine supplementation trials in humans have investigated effects on conditions such as carpal tunnel syndrome, pre-menstrual syndrome, sickness during pregnancy and hyperhomocysteinaemia. The majority of these trials have not been placebo controlled and have either not considered or not reported adverse effects in detail. The available studies are considered in detail in the review of vitamin B₆ (<http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers>) and the key studies for the risk assessment are discussed below.

Animal data

Symptoms of neuropathy have occurred at variable time intervals in different species following doses ranging from 50 mg/kg bw/day to 7000 mg/kg bw/day. Inter-species variability in response is apparent.

No effects on foetal development have been observed in animal studies. Doses of 250 and 500 mg/kg bw/day pyridoxine, administered intraperitoneally, produced histological changes in the testes of rats (reversible at the lower dose), and doses of 50 mg/kg/day administered intraperitoneally to female rats prevented prolactin release.

Carcinogenicity and genotoxicity

No published data on the carcinogenicity or genotoxicity of pyridoxine have been found.

Mechanisms of toxicity

Pyridoxal phosphate is thought to be responsible for the observed toxicity. Schwann cells in culture grow less well when provided with pyridoxal in the culture medium than when the vitamin B₆ source is pyridoxine. The addition of pyridoxal to the culture medium decreased cell survival even in the presence of an adequate concentration of pyridoxine, suggesting a possible neurotoxic action of pyridoxal. It is not known whether pyridoxal is cytotoxic to other cell types in culture.

Dose-response characterisation

The precise dose-response relationship between pyridoxine and peripheral neuropathy is uncertain in humans. Neuropathy has been associated with high doses of pyridoxine (generally over 2000 mg/day), but the duration of exposure is also important, with neuropathy occurring after long periods of exposure to lower levels (500 mg/day or less) of supplemental pyridoxine.

Vulnerable groups

No groups particularly vulnerable to pyridoxine-induced toxicity have been identified.

Genetic variations

No genetic variations which increase vulnerability to toxicity of vitamin B₆ have been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

Human data

Data are available from numerous human studies for consideration in the risk assessment of vitamin B₆. However, most of the available human data are unsatisfactory, with retrospective exploration of records, use of non-standardised end points and incomplete follow up. Other significant deficiencies were that the studies did not include adequate controls (similar patients who were not treated with vitamin B₆), were often performed in small groups using observational methods, and were of a duration of treatment (< 6 months) too short to reveal neurological effects, even at very high doses. In many studies adverse effects were not examined. Examples from the available database are described in more detail below.

Short term studies

Del Tredici et al., 1985

This report studied the effect of vitamin B₆ on 24 patients with carpal tunnel syndrome treated for 2-4 months with 150 or 300 mg vitamin B₆ daily. Vitamin B₆ was reported as having a beneficial effect on carpal tunnel syndrome, and no exacerbation of neurological symptoms or signs of peripheral neuropathy were reported. Distal motor latency was measured and patients completed a self-assessment questionnaire numerically ranking the severity of the symptoms. The short duration and small number of patients involved limit the usefulness of this study in setting a safe upper level.

Brush, 1988

In a retrospective survey of 336 women treated with pyridoxine alone or in combination with other agents, 5 subjects reported mild tingling and/or numbness at doses of 200 mg/day, which were described in the paper as 'definite side effects'. Similar side effects were not observed in an earlier

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group of women treated with up to 150 mg/day. No control group of patients unsupplemented with vitamin B₆ was included. This study does not form an adequate basis for setting a safe upper level because of the lack of detail in the reporting, particularly with respect to duration of treatment.

Brush et al., 1988

The effects of supplemental vitamin B₆ in 630 women suffering from premenstrual syndrome were described from a retrospective survey of clinical records. The patients reported taking daily doses of vitamin B₆ ranging from 40 to 100 mg early in the study and from 120 to 200 mg later in the investigation period. The highest dose taken was 100mg/day or less in 77% of the patients. Patients were reported to have taken vitamin B₆ for periods from three months to five years, but only 20% of subjects had continued treatment for more than one year. The authors reported that indigestion and nausea were 'probably genuine side effects' and that peripheral sensory neuropathy was not observed. The limitations of this study are that symptoms were reported from a retrospective investigation of records and inadequate details were included.

Bernstein and Lobitz, 1988

In an open study, 16 patients received 150 mg vitamin B₆ daily for 6 months for the treatment of diabetic neuropathy. It was reported that one patient developed increased photosensitivity with increased tanning on minimal exposure to sunlight, but this subject elected to remain in the study. The patients underwent a monthly clinical evaluation by a neurologist, including a detailed electrophysiological study of motor and sensory nerves. No deterioration of peripheral nerve function was observed, though examinations were completed after only 4 months of supplementation in 10 subjects and after 5 months in 5 subjects. The limitations of this study are the short duration of treatment, the small number of patients studied and the incomplete follow-up of symptoms.

Molimard et al., 1980

In a double-blind study, 69 medical students received a tablet of placebo, 50 or 250 mg vitamin B₆ twice a day for 10 days (total dose being 100 or 500 mg/day). The subjects were given a simple digit-coding task prior to treatment, immediately after treatment and 14 days later. The volunteers were also tested at the end of the treatment period on some numerical problems and on the content of the medical undergraduate course during the study period. Fifty eight of the volunteers completed the digit-coding tests, which showed a highly significant improvement with time (a learning effect) in all groups. There were no significant differences between groups in the uncorrected scores, but there was evidence of a dose-related decrease in the learning effect, which was highly statistically significant ($p < 0.002$) in the highest-dose group compared to the controls, but this was not statistically significant at the 5% level ($p < 0.07$) in the 100 mg/day group. No other differences were observed between the three groups. In a second experiment, a group of 30 patients were randomised to receive placebo, 20 mg or 1000 mg/day pyridoxine for 15 days with subjects given a variety of tests before and after treatment. At the high dose, an adverse effect was reported for word recognition, but not for word or visual memorisation. Performance in the visual retention test was worse in the high dose pyridoxine group after treatment. The extremely short treatment period and the small number of participants limit the usefulness of this study.

Berger et al., 1992

Doses of 1000 or 3000 mg/day pyridoxine were administered to three and two healthy volunteers respectively, until the development of symptoms of neuropathy in an experimental study. Symptoms occurred within 1.5 and 3.5 months in high-dose subjects. In subjects treated with 1000 mg/day

symptoms of neuropathy, indicated by numbness and pins and needles sensation in the toes, developed in two of the subjects after 4.5 and 7 months of treatment. Treatment of one subject was continued for over 14 months before quantitative sensory threshold test results became abnormal, an early indicator of neuropathy. An inverse relationship was observed between the daily dose calculated on a body weight basis, and the time taken for the development of toxicity. In other words as the dose decreased, the period of treatment before onset of adverse effects increased. Clinical symptoms continued to intensify for some weeks after pyridoxine was withdrawn. The very small number of participants involved in this study limits its usefulness in risk assessment.

Bernstein and Dinesen, 1993

This paper reported the effect of vitamin B₆ in the treatment of carpal tunnel syndrome. Sixteen patients received 200 mg vitamin B₆ per day for 3 months. No signs of peripheral neuropathy were found in the uninvolved ulnar nerves, and there was no evidence of new peripheral neuropathy during the 3 months of treatment. The limitations of this study are the short duration and the small number of patients involved.

Schaumburg et al., 1983

This paper describes case reports of seven patients who had ataxia and severe sensory nervous system dysfunction after vitamin B₆ consumption. Patients self-prescribed a maximum of 2 – 6 g vitamin B₆ daily. Only two of the seven patients started taking the vitamin at such high doses, while others began with doses of 50 to 100 mg/day. None experienced symptoms at doses below 2 g per day. Plasma pyridoxine was measured in one of the patients at the initial examination and found to be 30ng/mL three hours after the subject's usual daily dose of 4 g vitamin B₆. The reported duration of treatment ranged from two months to over three years. The small number of patients and the lack of reported details limit the usefulness of this study.

Long term studies

Parry and Bredesen, 1985

The paper describes 16 patients who developed neuropathy after taking high doses of pyridoxine (200-5000 mg/day) for several months or more. The patients developed unstable gait, perioral numbness and a 'stocking-glove' sensory loss followed. Discontinuation of pyridoxine was followed by improvement in symptoms. The authors believed that the toxicity of pyridoxine was manifest through an effect on the dorsal root ganglion. Most patients took 2000 mg/day or more pyridoxine (many of these had started at lower doses) and symptoms became apparent within a year of taking 2000 mg/day or more. One patient had taken 200 mg pyridoxine/day for 3 years and two others had taken 500 mg/day for 1-2 years. Although the duration of this study is adequate, a limited number of patients were studied and few details are reported.

Dalton and Dalton, 1987

This paper represents a follow-up study of data presented in a letter to the Lancet in 1985, which described sensory neuropathy in 23 out of 58 women with premenstrual syndrome, who had serum vitamin B₆ concentrations above the normal range (Dalton, 1985). Serum vitamin B₆ levels were measured in all women taking vitamin B₆ supplements at a private clinic. Patients (n=172) who had elevated serum vitamin B₆ levels (above the normal range in humans of 3.16 to 18 ng/mL) were specifically asked to report symptoms such as tingling in the fingers, which could be interpreted as evidence of sensory

neuropathy. The patients were all taking < 50 to < 500 mg/day vitamin B₆ for premenstrual syndrome. No control group of patients with similar premenstrual symptoms, but not taking vitamin B₆, were asked the same questions. Patients reported symptoms including paraesthesia, hyperaesthesia, bone pains, muscle weakness, numbness and fasciculation that were bilateral and most marked in the extremities. Neurological examinations were undertaken on those who reported symptoms, but neurophysiological tests were not undertaken. Findings on neurological examination included weakness, diminution but not loss of tendon reflexes, positive L'Hermitte's test and sensory loss in a stocking-glove distribution. Symptoms disappeared when vitamin B₆ was withdrawn and reappeared if treatment was resumed. Complete recovery occurred within 6 months of stopping vitamin B₆ treatment. Three women had subnormal serum levels of vitamin B₆ after stopping supplementation due to symptoms of sensory neuropathy. They were advised to take 50 mg vitamin B₆/day, but within a month they again experienced symptoms of neuropathy and had serum vitamin B₆ levels of > 18 ng/mL. The 103 women who presented with symptoms took a mean dose of 117 ± 92 mg vitamin B₆ for a period of 2.9 ± 1.9 years, and in 70% of these subjects, serum levels were > 34 ng/mL (the upper limit of testing). In contrast, the group which did not report symptoms, took a mean dose of 116 ± 66 mg vitamin B₆, for a period of 1.6 ± 2.1 years, and in 55% of these subjects, serum levels were > 34 ng/mL. The difference in duration of treatment, was statistically significant ($P < 0.01$). Although the duration of treatment and the measurement of plasma vitamin levels in this study were useful, the study has limitations when being considered for risk assessment. The lack of a control group and potential bias introduced by the focussed questioning of the patients on their symptoms detract from the quality of these data. It should be noted that muscle weakness has not been observed at higher doses in other studies.

Mitwalli et al., 1984

Twenty two male patients with kidney stones secondary to hyperoxaluria were given doses (250 – 500 mg/day) of vitamin B₆ for 8 months to 6 years (average 2.3 years). Seven subjects underwent nerve conduction studies. No neurological complications were reported in the group. The usefulness of the findings of this study for risk assessment is limited by the low number of patients involved.

Hawkins, 1986

A lower than expected incidence of tardive dyskinesia was reported in a total of 58,139 schizophrenic patients who had been treated by 80 physicians, in some cases for many years, with neuroleptics (phenothiazines and/or haloperidol) and with high doses of a mixture of vitamins. The vitamin regimen consisted of three daily doses of vitamin C (1000 mg), vitamin B₆ (200 mg), vitamin E (200 IU) and either nicotinic acid or nicotinamide (1000 mg). This data set is of limited value for several reasons: there is a lack of detail, the results have not been published in a peer-reviewed journal, there was no check on compliance (which is a problem in such patients), the primary endpoint (tardive dyskinesia) is not relevant to vitamin B₆ neuropathy, the elicitation of minor vitamin B₆-related symptoms in schizophrenic patients would have been difficult, and any effect of vitamin B₆ might have been masked by the neuroleptic drug treatment and/or the very high doses of the other vitamins. In consequence, the usefulness of these observations for risk assessment is limited.

The study which reports neuropathy at the lowest dose (50 mg/day) is that of Dalton and Dalton (1987), but this investigation is flawed in a number of ways. For example, there was no control group, and since subjects were questioned about their symptoms, reports may be biased. However, this study has the advantage that plasma levels of the vitamin were measured. In women with elevated plasma levels, longer exposure was associated with clinical symptoms and in the absence of better quality data to confirm safety, it is not possible to dismiss this investigation. Brush (1988) and Parry and Bredesen (1985)

reported neuropathy at doses of 200 or 500 mg/day, the latter study involving exposure of several years' duration. However, small numbers of patients were involved and few data were provided. Other studies which investigated the effects of low doses of vitamin B₆ (Del Tredici *et al.*, 1985; Bernstein and Lobitz, 1988; Bernstein and Dinesen, 1993) were somewhat better conducted but did not consider exposure of sufficient duration. For example, in Bernstein and Lobitz (1988) patients received 150 mg/day for 6 months, in Del Tredici (1985) patients received 150 or 300 mg/day for 2-4 months and in Bernstein and Dinesen (1993) the subjects received 200 mg/day for 3 months. These studies did not have placebo control groups and involved small numbers of patients, as well as being of durations that were insufficient for the development of symptoms, even had the doses been higher. Thus while the results of these studies are negative, they are not necessarily incompatible with those of Dalton and Dalton (1987).

Animal data

In many of the available animal studies vitamin B₆ was administered by injection. Whilst these studies confirm that pyridoxine neurotoxicity is dose- and time-dependent in both rats and dogs, the data are not directly comparable to those generated by exposure via the oral route. In contrast to the majority of the human data, the animal studies described below were performed under controlled conditions making them useful for consideration in risk assessment. Small numbers of animals were involved, as is common practice for studies conducted in dogs.

Phillips et al., 1978

Pyridoxine hydrochloride was administered orally in gelatine capsules (0, 50 or 200 mg/kg bw/day) to three groups of female beagles (four control and five per treatment group) over 100-112 days. Four of the five animals in the high dose group showed signs of ataxia and loss of balance after 45 days of treatment, while the fifth showed clinical signs after 75 days. Clinical signs of toxicity were not observed in the 50 mg/kg/day group, but bilateral loss of myelin in the dorsal nerve roots was observed histologically.

Hoover et al., 1981

Three adult beagle dogs (with a fourth dog serving as a control) received pyridoxine hydrochloride in gelatine capsules, 5 mg/kg bw/day for the first week, 100 mg/kg bw/day for the second week and 150 mg/kg bw/day from the 15th to the 100th day of the experiment. Neurological disease, characterised by proprioceptive defects, developed in each pyridoxine-treated dog and occurred in two dogs during the fourth week and in the third dog during the eighth week of administration. The dogs had spastic, dysmetric leg movements and lacked apparent sense of motion or position of the legs. This was characterised ultrastructurally by degeneration of axons, loss of axons, collapse of myelin sheaths, degeneration and loss of myelin and astrocytic scarring on histological examination.

Krinke et al., 1980

Six beagle dogs were administered 300 mg/kg bw/day pyridoxine hydrochloride in gelatine capsules, in addition to a balanced diet. The animals were examined in comparison with two control dogs. Within 9 days the treated animals developed a swaying gait, and eventually became unable to walk, but had no observable muscle weakness. Morphological examination showed widespread neuronal degeneration in the dorsal root ganglia and the Gasserian ganglia. Degeneration of sensory nerve fibres was apparent in peripheral nerves, dorsal columns of the spinal cord and the descending spinal tract of the trigeminal nerve.

Exposure assessment

Total exposure/intake:

Food Mean: 2.0 mg/day
 97.5th percentile: 3.9 mg/day (NDNS, 1986/87)

Supplements up to 100 mg/day (Annex 4)

Estimated maximum daily
 exposure: 3.9 + 100 = 104 mg

No potential high intake groups have been identified.

Risk assessment

The key adverse effect, for vitamin B₆ is neuropathy, which has been demonstrated in both humans and laboratory animals. The effect occurs after consumption of high doses and/or long duration. Generally the symptoms are reversible once the exposure is stopped but in some cases involving high doses, the effects are irreversible. Progressive sensory ataxia occurs, presenting initially as unstable gait and numb feet, then numbness in the hands, followed by profound impairment of position sense and vibration sense in the distal limbs. The senses of touch, temperature and pain are less affected.

Data from animal studies also demonstrate neurotoxicity, although some species differences are apparent. Doses as low as 50 mg/kg bw/day have been associated with a loss of myelin. Subtle effects such as changes in startle response have also been observed. The animal data also suggest that duration of exposure is important in the response to vitamin B₆.

ESTABLISHMENT OF SAFE UPPER LEVEL

As discussed above, the available human data are not adequate for risk assessment and the Safe Upper Level has been based on the most appropriate of the studies performed in animals under controlled conditions.

Phillips *et al.* (1978)

LOAEL: 50 mg/kg bw/day, based on the study by Phillips *et al.* (1978) in dogs

Uncertainty factors: 3 for LOAEL to NOAEL extrapolation

10 for inter-species variation

10 for inter-individual variation

Safe Upper Level (for daily consumption over a lifetime): $50/300 = 0.17$ mg/kg bw/day supplemental pyridoxine (equivalent to 10 mg/day for a 60 kg adult)

Excessive quantities of vitamin B₆ result in peripheral neuropathy in both animals and humans. The effect is dependent on both the dose and the duration of exposure.

In order to determine the levels at which vitamin B₆ could be safely taken by the entire population over a lifetime, large well-controlled studies with careful symptomatic observation and attention to critical endpoints are required. Unfortunately much of the available data from studies in humans are unsatisfactory with retrospective exploration of records, use of unstandardised end points and incomplete follow up, often of small observational groups with short durations of treatment (< 6 months) and without adequate control groups.

Despite the limitations in design of the human studies, the available data clearly indicate that pyridoxine causes neuropathy in humans and that the duration of exposure as well as dose is important. Therefore, in the absence of better quality data the reports of toxicity following long, low level exposure to vitamin B₆ cannot be entirely dismissed. Overall, the human data are inadequate to establish a Safe Upper Level, since the effect levels are unclear and the studies at low levels of intake are of limited quality.

Neuropathy is also observed in laboratory animals, and the data confirm the importance of dose and duration in determining the effects of vitamin B₆. In the absence of reliable human data at low levels of exposure, the Safe Upper Level is based on animal data, in which histological changes were apparent in the nerves of dogs treated with 50 mg/kg bw/day for 100-112 days (Phillips, 1978). Clinical signs of toxicity were not apparent in this group but were observed in the high dose group which received 200 mg/kg bw/day. Using uncertainty factors of 300 (consisting of 3 for LOAEL to NOAEL extrapolation of a histopathological change, 10 for inter-species and 10 for inter-individual variation) a Safe Upper Level of 0.17 mg/kg bw/day can be derived. This relates to supplemental pyridoxine because the basal pyridoxine content of the diet in the key study is unknown. This SUL is equivalent to 10 mg/day in a 60 kg adult. These uncertainty factors are appropriate because the LOAEL in the dog related to a sub-chronic study and therefore may have underestimated the toxicity during chronic exposure. The need for an inter-species factor is supported by the fact that the LOAEL dose in dogs (50 mg/kg bw/day) is equivalent to an intake of 3000 mg per day in humans, which would produce severe toxicity in humans, suggesting that humans are probably more sensitive than dogs to these effects. Finally, the factor for human variability is necessary to allow for the greater size and diversity of the human population compared with the small number of dogs (n=5) studied by Phillips *et al.* (1978).

In humans, a supplementary dose of 10 mg/day represents a clear SUL, with no adverse effects being anticipated over a lifetime's exposure. Doses of 200 mg/day vitamin B₆ or more taken for long periods are associated with reports of neuropathy in some human subjects. The effect of taking vitamin B₆ at doses between 10 and 200 mg is unclear. The risk posed by such exposure in the short term may be negligible, but the available data do not allow identification of a dose or duration of exposure above the SUL that would be of negligible risk.

It is unfortunate that no reliable and controlled studies have been conducted in the past 5 years to establish whether intakes between 10 and 200 mg/day are safe in the long term.

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