

# VITAMIN B6

- Why is this vitamin being restricted?
- Safety limits on doses

Recent Government plans for legislation to limit levels of vitamin B6 in dietary supplements sold under food law have caused controversy within Parliament and elsewhere. This decision was based on expert advice that high levels (above 50 mg/day) of vitamin B6 may cause harmful side-effects, but the scientific basis of this advice has since been challenged.

*This note looks at the scientific evidence and uncertainties concerning the effects of different doses of vitamin B6, and the issues that arise.*

## BACKGROUND

In June 1997, the Department of Health's (DH's) Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) released a Statement on Vitamin B6 Toxicity, recommending that the maximum daily intake of B6 from dietary supplements should be 10 mg/day. This was the second time that COT had reviewed the evidence concerning the safety of vitamin B6 (prompted by concerns expressed by the Consumer's Association), and this review included consideration of over 100 national and international scientific papers, as well as evidence submitted by interested parties (e.g. industry and nutritional therapy /alternative medicine interests).

Vitamin B6 is sold both as a medicine and as a food supplement, and the COT recommendation had implications for both:

- **Food** - on July 4 1997, the Government announced plans to draw up legislation under the Food Safety Act 1990 to control levels of vitamin B6 in dietary supplements sold under food law. This announcement followed advice from the Food Advisory Committee (FAC), which endorsed the COT statement and recommended that dietary supplements containing B6 should carry a warning label on the risk of harmful effects at intakes above 10 mg/day.
- **Medicine** - B6 is also licensed for use as a medicine to treat certain conditions, and COT's advice was also considered by the Committee on the Safety of Medicines (CSM) and the Medicines Control Agency (MCA). The CSM advised that medicines containing up to 10 mg/day should remain on general sale, those with 11-49 mg/day should be 'pharmacy only' medicines (i.e. not available via self-selection, but available 'over the counter' with sales supervised by a pharmacist), and those containing 50 mg/day or more should be 'prescription only' medicines. The MCA is currently reviewing licensing arrangements.



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Table 1 EFFECTS OF VITAMIN B6 (HUMANS)

Dose	Effect
0 mg/d	Deficiency symptoms (e.g. mouth sores, nausea, anaemia, convulsions)
1.2-1.4 mg/d	Reference Nutrient Intake (RNI) for adults
50-200 mg/d	'Grey area' where some studies (e.g. Dalton) show various (reversible) symptoms in women receiving B6 for pre-menstrual syndrome (PMS), and others not
200 mg/d or more	Associated with (reversible) sensory neuropathy in several studies
2000-7000 mg/d	Causes sensory neuropathy, which may include permanent nerve damage

COT's recommendations have triggered a number of other developments. For instance, the Royal Pharmaceutical Society of Great Britain (RPSGB), wrote to 12,500 pharmacists in Britain advising them to implement the CSM's recommendations immediately, and supermarkets and health food shops have withdrawn high dose dietary supplements for B6. The scientific basis of the advice has been questioned by the Council for Responsible Nutrition (CRN) and others, and some 100 MPs have signed an Early Day Motion opposing the proposed legislation.

## THE SCIENTIFIC EVIDENCE

Known effects of different doses of vitamin B6 on **humans** are summarised in **Table 1**. As explained in more detail in **Box 1**, B6 is one of a dozen or so different vitamins required by the body in small amounts to prevent various deficiency symptoms (in the case of B6, these include skin lesions, anaemia, muscle cramps and convulsions). The amount of B6 required varies (according to age, gender and the amount of protein in the diet), but the RNIs<sup>1</sup> for this vitamin in the UK are 1.2 mg/day for adult women and 1.4 mg/day for men. Intakes significantly below these figures may lead to deficiency symptoms, although the relative abundance of vitamin B6 across a wide range of foods means that such conditions are very rare.

At the other end of the scale, there is general agreement that very large doses are toxic. In a 1983 study, 7 patients taking from 2,000 to 7,000 mg/day of B6 developed **sensory neuropathy** - a condition caused by damage to the nervous system and characterised by symptoms such as pins and needles, numbness, clum-

<sup>1</sup> Reference Nutrient Intakes - the amount which is enough to meet the needs of nearly all (97%) members in a given group - set by the DH's Committee on Medical Aspects of Food and Nutrition Policy (COMA).

**Box 1 VITAMIN B6 IN THE DIET**

Vitamins are chemicals that are essential for life, but which the body cannot manufacture for itself and which must thus be provided in the diet. To date, some 13 different vitamins have been identified. These chemicals are needed because they perform specific jobs within the body. In the case of the six closely related chemicals (pyridoxine, pyridoxal, pyridoxamine and their respective phosphates) included in the generic term **vitamin B6**, this function is to act as co-factors for a wide range of different enzymes. Many of these are involved in the metabolism of proteins and amino acids (the building blocks from which proteins are made), so the amount of B6 required depends on the amount of protein in the diet. Experts agree that the average requirement is around 15µg B6 per g protein per day, which translates to around 1.4 mg per day for the average adult male.

Although only required in small amounts, insufficient vitamins in the diet can cause a range of **deficiency diseases**. With B6, deficiency symptoms include mouth sores, nausea, anaemia, and convulsions. However, such deficiencies are rare since a normal, varied diet provides more than enough B6 to prevent deficiency (fish, meat, poultry, whole grains, legumes, potatoes, nuts, bananas and brewers yeast are all sources of B6).

business, etc. Withdrawal of high doses led to most patients recovering most of their sensory nerve functions, but tests revealed that some had suffered permanent damage. Such studies have focused attention on the growing market in vitamin supplements sold under food law where an estimated 3-4 million packs of B6-containing supplements with doses of 40-50 mg/day and above are consumed in the UK annually. Some of the higher dose rates are 250 mg/day - far higher than the levels achievable through normal dietary intakes, and over 200 times the RNI for an adult woman.

Given these consumption patterns, the key question is whether adverse effects may result from dose rates in the range 50-200 mg/day. Here, one study conducted in 1987 (the 'Dalton' study) found evidence of adverse effects among 172 women taking doses from around 50 to 500 mg/day of B6 for PMS. Symptoms such as leg muscle weakness, bone and chest pain, loss of libido developed slowly and the authors diagnosed high rates of sensory neuropathy in 60% of the women exhibiting raised serum levels of B6. Other studies however fail to find deleterious effects at such levels - a 1988 study of 630 patients receiving doses from 40-200 mg/day found no symptoms consistent with sensory neuropathy, while a recent consumer survey conducted by AGB Healthcare found that people taking B6 supplements at up to 200mg/day were no more likely to suffer from symptoms of marginal neuropathy (tingling fingers, restlessness) than the population as a whole.

COT also found evidence of **adverse reactions** among people taking B6 medicines prescribed by their doctors. Between July 1963 and July 1997, the yellow card scheme run by the MCA received some 160 reports (each relating to a single patient) of reactions associated

with medicines containing only B6. In total, these involved some 411 different adverse reactions (each patient typically showing several reactions). Medicines containing vitamin B6 in conjunction with other vitamins and minerals were associated with a further 490 patients over this period, accounting for some 1,152 adverse reactions. Some were associated with doses of below 100 mg/day.

A parallel insight into the effects of large doses comes from studies in **animals**, where high doses of B6 cause adverse effects, including lack of muscular co-ordination and muscle weakness. As summarised in **Table 2**, it is well established that daily doses of 100-1,000 mg of B6 per kg of bodyweight can cause sensory neuropathy in both rats and dogs. The lowest daily dose causing adverse effects in animals is 50 mg/kg when given to dogs for 16 weeks. All other things being equal, this is equivalent to a daily dose of ~3,000 mg for a person of average weight (60 kg). One study found no effect when 20 and 25 mg/kg/day was given to dogs and rats respectively for 80 days, although COT expressed doubts about this result (the paper was published in 1940, and experimental details were sparse). Little evidence is available concerning the effects of lower doses (e.g. 1-10mg/kg/day) on animals.

**DERIVING THE 10 MG/DAY LIMIT**

The original COT recommendation of a cut-off level of 10 mg per day of B6 from dietary supplements was based on the studies described above. The actual figure of 10 mg can be derived from the animal studies, by taking 50 mg/kg of bodyweight as the lowest level at which adverse effects had been observed:

- First the lowest adverse effect level is divided by a safety factor of 10 for using animal data - this gives 5 mg/kg/day;
- This is then divided by a second factor of 10 to protect sensitive individuals (0.5 mg/kg/day);
- A further factor of 3 is used because the standard is based on the lowest observed adverse effect level (to give 0.167 mg/kg/day);
- 0.167 mg/kg/day is equivalent to 10 mg/day for an average bodyweight of 60 kg.

COT sees this conclusion of a safe upper limit of 10 mg/day as being consistent with the results from human studies. For instance, they argue that the lowest reported adverse effect level in humans is 50 mg/day (the Dalton study), so that setting the upper limit at 10 mg/day gives a 5-fold safety factor between the doses on general sale, and the lowest levels thought to cause toxic effects in humans. COT also points out that bodies such as the World Health Organisation / Food and Agriculture Organisation s' Joint Expert Committee on Food Additives routinely use safety factors of 100 on animal data (10 to account for animal-human

Table 2 EFFECTS OF VITAMIN B6 IN ANIMALS

Animal Dose mg/kg/d	Equivalent* human dose mg/d	Effect
100-1,000 50	6,000-60,000 3,000	Neuropathy in dogs and rats Minimum dose causing neuropathy in dogs
20-25	1,200-1,500	No effect in dogs or rats (but doubt over study)
1-10	60-600	Dose range of most interest, but lack of studies

Note: \*assuming bodyweight of 60kg

differences and 10 for variations in people's sensitivity) when setting Provisional Maximum Tolerable Daily Intakes for dietary components. Moreover, such calculations are usually based on the **maximum dose causing no adverse effects** in animals. When such information is not available and safety limits are based on the **minimum dose known to cause adverse effects**, an additional safety factor is introduced (usually between 2 and 5). Finally, the adverse reports from doctors added weight to concerns over possible adverse effects in the 50-200 mg/day range.

## ISSUES

The key scientific points in the debate are thus:

- The central plank on which COT's recommendation is based - a lowest observable adverse affects dose of 50 mg/kg/day in animals - is not contested.
- The 10 mg/day limit for humans can be derived from the animal data using standard, internationally agreed, toxicological protocols.
- Studies of B6 toxicity in humans give conflicting results. All agree that small (i.e. 1-2mg/day) doses are needed to maintain health and that large (i.e. g/day) doses are harmful. Evidence on direct effects of doses from 50-200 mg/day is more equivocal.

The health-food industry and others (including nutritional therapy/alternative medicine interests, as well as some scientists) do not challenge the arithmetic but rather question two basic aspects of COT's advice<sup>2</sup>:

- the appropriateness of using standard toxicological procedures to derive acceptable daily intakes for nutrients such as vitamins;
- the quality of some of the evidence regarding toxicity and benefits in humans.

### **Appropriateness of the Regulatory Approach**

COT sees no scientific distinction between B6 and other chemicals (e.g. food contaminants, additives) and sees it as being entirely appropriate to derive safety limits for B6 in the 'normal' way. It further points out that vitamin B6 is by no means unique in having been treated in this way - safety limits have recently been

2. There is also the argument that applying similar safety factors could lead to restrictions on the sale of coffee (because of its caffeine content), fruit juices (vitamin C), wine and beer (alcohol), etc. The counter to this is that the safety factor was not applied to vitamin B6 in food, but rather to chemical preparations sold separately.

### **Box 2 WHY PEOPLE TAKE HIGH DOSES OF VITAMIN B6**

People take higher doses of vitamin B6 for a range of reasons, some as medicines prescribed by their doctors, others as dietary supplements purchased from health shops, supermarkets, etc.

As far as **medicinal uses are concerned**, there are currently 83 licensed medicinal products containing vitamin B6 in one form or another in the UK, licensed for a number of indications including:

- sideroblastic anaemia (defective production of haem);
- pyridoxine deficiency states;
- isoniazid neuropathy (where prolonged courses of anti-bacterial drugs which reduce B6 levels in the body lead to deficiency states);
- parenteral nutrition (B6 supplementation is required when parenteral nutrition is being administered);
- hyperoxaluria (a range of genetic B6 dependency syndromes).

Only relatively small numbers of people are affected by such medical conditions. Many more take higher doses of B6 in the form of **dietary supplements** with daily doses of up to ~200 mg. For instance, a recent survey of 1,671 vitamin B6 consumers conducted by AGB Healthcare showed that around two thirds took B6 supplements every day, the vast majority at doses of 50-200 mg/day. Such doses have been claimed to benefit people suffering from a range of different conditions including pre-menstrual syndrome (PMS), carpal tunnel syndrome (a repetitive strain injury affecting nerves in the wrist) and asthma. Of these, the survey found that roughly 1 in 2 consumers were taking B6 primarily for PMS, although the extent to which B6 supplements actually do benefit people suffering from such conditions remains unproven in clinical trials (some studies show benefits, others not). In addition to consumers using B6 sold under food law to 'treat' medical conditions, the survey found that nearly half the consumers were taking B6 supplements to 'boost their energy' or as part of a wider vitamin regime aimed at improving their general well-being.

proposed for two essential vitamins/minerals - iodine (in milk) and vitamin A (for pregnant women) - using exactly the same toxicological approach.

Others, such as CRN point out that the standard toxicological protocols were designed to establish an absolute safe level for the intake of substances such as pesticides which can only be harmful. They draw a distinction between such substances and nutrients such as B6 which have beneficial effects at certain levels. They argue that rather than deriving absolute safety limits from animal data, the question should focus on establishing the upper safe level of intake in humans. In other words, greater weight should be given to the results of human experience rather than extrapolation from animal experiments (where large safety margins are used to guard against the danger of long-term effects such as cancer occurring as a result of low exposures over long periods). This places the focus onto the balance of benefits and toxic side-effects from clinical studies and anecdotal experience.

### **Balancing Benefits and Toxicity**

As outlined in **Box 2**, some people take high doses of B6 as medicines prescribed by the doctors, others as di-

etary supplements sold under food law. As far as medicines are concerned, the benefits of B6 for treating medical conditions such as deficiency states and genetic dependency syndromes are well established. The use of B6 to treat conditions such as these is not contentious - products are licensed as medicines, and prescribed by doctors. CSM advice (if implemented) would mean that higher doses will still be available to people who need them through doctor's prescriptions. Given the concerns over the toxicity of B6, many see it as being entirely appropriate that people taking large doses should be medically supervised.

For dietary supplements however, quantifying the benefits of B6 has not been straightforward, with some studies supporting beneficial claims for conditions such as PMS, and others finding no effects. For instance, the latest (September 1997) edition of the British National Formulary (a medical reference book widely used by doctors) notes that B6 "*has been tried in a wide variety of other disorders, including the premenstrual syndrome, but there is little sound evidence to support the claims*".

With uncertainty over the claimed benefits of dietary supplements, attention returns to exactly what levels may cause adverse effects in human. Here a key point at issue is the interpretation of the 'Dalton' study - where doses as low as 50 mg/day were found to cause symptoms in women when taken over very long periods. This has been criticised on:

- **Study design** - the way in which participants were selected, the fact that all were suffering from a medical condition anyway (PMS), the lack of an appropriate control group, etc.
- **Nature of symptoms** - the types of symptoms most frequently reported (leg muscle weakness, bone pain, chest pain, loss of libido) are not the same as those characterising sensory neuropathy (i.e. pins and needles, sensory loss, clumsiness). This has led some experts to question the high rate of diagnosis of sensory neuropathy made by the researchers.
- **Clinical experience** - a number of doctors see the finding that 50 mg/day can produce adverse effects as at odds with their own clinical experience, where they prescribed doses of up to 200 mg/day over comparable periods without seeing such effects.

COT acknowledges that this study has certain "*methodological deficiencies*", but points out that the committee's recommendations were not made on the basis of the Dalton study alone, seeing it as "*unwise to ignore this evidence in the light of other supporting human and animal data*", and arguing that the **totality** of the evidence suggests a recommended daily intake limit of 10 mg/day (a level which still allows intakes several times higher than the RNI). With the uncertainty over the claimed benefits, bodies such as the FAC see no clear

reason to disregard the advice on toxic effects and have endorsed the changes proposed by COT.

## OVERVIEW

The problems discussed above largely arise because dietary supplements fall into a regulatory 'no mans land' between foods and medicines. Medicines are very closely regulated, with manufacturers having to conduct clinical trials to prove the efficacy of their products before a license is granted. Food law on the other hand expressly forbids medical claims to be made for food products. Dietary supplements fall in between these two - people who take B6 supplements perceive a wide range of benefits (whether in the management of medical conditions such as PMS, or in the more general sense of improved well being, boosted energy, etc.), few (if any) of which have been clinically proven.

**The key policy issue is to what extent the Health Food industry should have to substantiate beneficial claims and to safety test its products, in the same way as is required for medicines and food additives/contaminants.** Those who see little evidence of general benefits of high doses of B6 argue that it should be treated as any other potentially toxic food additive or contaminant, and the regulatory system established to protect the consumer should not apply one set of rules for substances which enjoy public support and another for those which the public sees as only harmful. Treated this way, standard toxicological procedures will deliver a maximum safe limit of around 10 mg/day.

Those that value the benefits of B6 supplements more highly see the need for a flexible approach which does not rely on the usual safety margins. For instance, a recent CRN symposium concluded that an appropriate safe upper level would lie between 100 and 200 mg/day. This would, in effect, leave consumers to judge for themselves the balance of perceived benefits against any adverse side-effects.

Similar debates will no doubt emerge in the coming years as increasing numbers of functional foods (i.e. for which health claims are implied) find their way onto the market, and this has led to calls for a dialogue between consumers, scientists, government and industry to establish the best way forward in determining safe upper limits for vitamins and minerals. Parliamentarians may thus need to consider where the balance of responsibility should lie between consumers, the health food industry and regulators. In this respect, any national debate will need to take into account moves within the EU on possible regulatory approaches, and MAFF has recently circulated for consultation a discussion paper on "fortified foods and dietary supplements".