Vitamin B_6: Extract of Submission to the UK's Food Standards Agency

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Extract of Submission to the UK's Food Standards Agency by the Institute for Optimum Nutrition (ION)

In May, 2003, the British Food Standards Agency's Expert Group on Vitamins and Minerals (EVM) proposed a Safe Upper Level (SUL) for vitamin B_6 of 10 mg. This had been proposed, and blocked, in 1988. We believe the basis for arriving at this figure is scientifically flawed, and rightly invoked a considerable scientific and consumer backlash when first proposed in 1998. The human equivalent (allowing a factor of 100) lowest observable adverse effect level (LOAEL) of 30 mg/day established from Phillips' dogs study[1] and the 50 mg/day LOAEL suggested by Dalton and Dalton[2] have both been scientifically discredited, in the former by the authors of the study themselves and in the latter by overwhelming scientific consensus. Below, these and the remaining 'key studies' used in the EVM assessment are revisited briefly before new and existing evidence, not previously considered by the EVM in its assessments of vitamin B_6, is presented with a view to enabling a more accurate human-based No Observable Adverse Effect Level (NOAEL), and therefore SUL, to be established.

1.1 The Animal Study Used to Set the SUL is Inappropriate

The currently proposed SUL of 10 mg/day for vitamin B_6 is based almost entirely on a 24 year old study by Phillips et al.[1] in which 5 beagle dogs demonstrated adverse effects at a dose of 50 mg/kg bw/day administered for 3-4 months. While we welcome the EVMs efforts to establish a clear SUL, we assert that it is inappropriate to place so much reliance on animal data when such a large body of human data and clinical evidence upon which there is scientific consensus is available (see below).

Furthermore, numerous scientific flaws exist in the method used to extrapolate this animal data to humans, and the study coordinator, Dr. Ian Munro, has protested that the division factor of 300 is "inappropriately large" because vitamin B_6 is an essential nutrient and also because dogs handle vitamin B_6 in the same way as do humans.[3] We understand that safety factors of this magnitude were designed with regards to chemicals that are foreign to the body such as pesticides, drugs and food additives, and are not in accord with the WHO guidelines relating to toxicity assessments of nutrients and substances that are normal body constituents:

"The use of standardized safety factors based on no-observed-effect levels for establishing the acceptable level of use of food additives is a crude procedure...If toxicity and dose-response effects in human beings are known, such data should take precedence over extrapolation from animal studies...A safety factor of 100 should not be considered immutable...A lower safety factor may...be appropriate when the additive is...metabolised into normal body constituents."[4]

Dr. John Mills, another co-author of the Phillips study has been quoted as saying "to make judgements on this study of a few dogs and to extrapolate to humans is utter nonsense. Anyone who defends that would be the laughing stock of the scientific community."[5] The use of human data should clearly take precedence over extrapolation from animals.

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1.2 The Discredited Dalton and Dalton 1987 Study

The EVM recognises that the Dalton and Dalton study is "flawed in number of ways," and go on to assert that "In the absence of better quality data, it is not possible to dismiss this investigation."

However, the overwhelming scientific consensus on this study is that it is so flawed that it must be dismissed. Since the publication of this study peer review has been extensively and often savagely critical and has entirely rejected the conclusions of this study. The reasons are many, including the asking of leading questions, which would be likely to bias results. The EVM draft report concedes this point, stating "Since the subjects were questioned about their symptoms, reports may be biased."

On the few occasions when vitamin B_6 was stopped and then restarted, the rechallenges were not conducted in a blinded fashion. The study hinged largely on the accuracy of recall of participants, which is unlikely to have been reliable. No attempt appears to have been made to validate stated dosages or durations of treatment. Dr. Dalton herself states that "there may have been inaccuracy in the patient's recall of the exact dose and duration of B_6 intake when the period of ingestion exceeded five years." The symptoms observed had no dose-response relation to pyridoxine intake.

The National Academy of Sciences Institute of Medicine, in their assessments of SULs in 1998,[6] excluded the Dalton study on scientific grounds, citing methodological flaws. They state "…the weaknesses of this [Dalton and Dalton] study and the inconsistency of the results with the weight of the evidence pertaining to the safety of higher doses of vitamin B_6 rule out the use of these data..."

The study is unrepresentative. No other study has reported comparable findings. To support SUL proposals in any way with this aberrant and highly flawed study is indefensible.

1.3 Scientific Evidence on Vitamin B_6

So what evidence is available on the safety of vitamin B_6? The EVM draft report lists, in addition to the two discredited studies mentioned above, seven "key studies for the risk assessment," all with humans. It was concluded from these and the Dalton and Dalton study that "the human data are inadequate to establish a SUL." If it is accepted that duration is as important as dose, no long-term NOAEL can be determined from the specified "key studies", though a long-term LOAEL is suggested by Parry and Bredesen's study,[7] specifically 200 mg/day, administered over a period of 1-3 years.

Yet this study appears incongruous with the rest of the scientific data, and is specifically criticised by Cohen and Bendich's review of the evidence,[8] who point out the lack of placebo control, the potential for inaccurate recall of dose, and the lack of clinical examination for half of the subjects involved. It cannot therefore be taken in isolation and the full body of scientific evidence must be considered in the setting of a SUL.

Below are listed further studies and reviews of the available human data not included in previous assessments by the EVM (including the extensive list in the document EVM/00/19), provided to enable a human-based NOAEL, and therefore SUL, to be established. Other reviewers, aware of the scientific shortcomings of the data relied upon by the EVM, have determined a NOAEL of 200 mg/day.[9] It can be seen that the overwhelming scientific consensus is that the SUL for vitamin B_6 is in the range of 100-200 mg/day.

A retrospective study conducted by the Institute for Optimum Nutrition in 2002, involving 563 patients taking between 30 and 250 mg of vitamin B_6 daily for 3 months to 42 months supports a NOAEL of 100 mg.

Neurologist Dr. Allan Bernstein followed 70 patients taking 100-150 mg/day vitamin B_6 for up to ten years. He reports

"Our clinical experience supports the conclusion that doses of 150 mg/day taken over a period of up to ten years does not produce neurotoxicity. Our conclusion is backed by electrophysiologic testing of nerve conduction. A review of the literature and an extensive personal experience in the clinical use of vitamin B_6 suggests that long-term safety exists at oral doses of 200 mg or less."[10]

Dr. David Hawkins initiated a multicentre study involving a variety of nutrients including vitamin B_6 at an average dose of 600 mg/day taken over many years. Covering some 58,000 patients, none of the 80 participating clinicians reported neurotoxicity.[11]

Doctors Herman Baker and Oscar Frank gave six elderly subjects 225mg/day vitamin B_6 for one year, reporting "produced no neuropathy."[12]

Doctors Marvin Cohen and Adrianne Bendich reviewed the available data on vitamin B_6 and concluded "Doses less than 500mg per day appear to be safe on the basis of literature reports where the compound was administered for periods ranging from 6 months to 6 years." They are particularly critical of the Dalton and Dalton study and various aspects of the Parry and Bredesen study. In a subsequent study by the same authors, "administration of 800 mg of vitamin B_6 per day for 17 months…was not associated with neuropathy."[13]

Professor Karl Bassler was commissioned by the German Research Council to review the safety of vitamin B_6 and reports "In view of the widespread use of vitamin B_6, reports of sensory neuropathy are not numerous; moreover, there are many reports stressing the absence of toxic side effects. It would appear that long-term administration of up to 200 mg daily may still be considered safe."[14]

Dr. John Marks, in a review of vitamin safety, concluded that the threshold for vitamin B_6-induced neuropathy lies above 500 mg/day, and the safe upper level for prolonged administration to be around 200mg/day.[15]

Dr. John Hathcock reviewed the efficacy and safety of several vitamins and minerals, appraising the data utilised for the selection of LOAEL and NOAEL values. For vitamin B_6 the data revealed a LOAEL of 500mg/day and a NOAEL of 200mg/day.[9]

1.4 Proposed SUL for Vitamin B_6 of 100 mg/Day

Based on the new data presented by the Institute for Optimum Nutrition and the existing evidence previously overlooked by the EVM, the Institute for Optimum Nutrition proposes a SUL for vitamin B_6 of no less than 100mg/day. In the United States the highly respected National Academy of Sciences Institute of Medicine has determined an adult safe upper level of 200 mg/day (see www.ion.edu). Even withstanding the 200 mg LOAEL in the criticised Parry and Bredesen study,[7] a SUL of 100 mg/day allows a considerable safety factor for a normal body constituent such as vitamin B_6.

1.5 What Would be the Effect of Retaining the Proposed 10 mg/day SUL?

While the EVM document states that "the efficacy of vitamins and minerals has not been considered since such effects would be classified as medicinal and would be within the remit of the MCA," it also asserts that "Nutritional need was taken into account to ensure that Safe Upper Levels were not set at a level below dietary requirements." It is the view of the Institute for Optimum Nutrition that setting SULs without regard to optimum levels or varying requirements of subgroups of the population is itself unsafe, and the proposed SUL of 10 mg for vitamin B_6 provides a good example of this. The draft document statement "Pyridoxine deficiency is unusual in humans" is open to question, and important in determining the risks of setting the SUL too low. It is the view of the Institute for Optimum Nutrition that the SUL for vitamin B_6 at 10 mg/day would

hinder the health of a large number of people for whom supplementation at levels higher than this, up to 100 mg/day, is necessary to maintain optimum health. Specific examples of subgroups of the population for whom this is the case are given below.

Vitamin B_6 Deficiency is Common

Vitamin B_6 is present in a lot of foods but, unfortunately, processing, canning and freezing destroys much of it. Many people are therefore deficient. In the U.S.A., a Nationwide Food Consumption Survey (1980) showed that over half of all Americans weren't getting enough B_6 in their diets. In the UK, recent National Food Surveys also indicate that the average daily intake of vitamin B_6 is often lower than the EU recommended daily allowance.

Vitamin B_6 Deficiency Raises Homocysteine Levels and CHD Risk

The EVM draft report states "pyridoxine deficiency may be a risk factor in hyperhomocysteinaemia which is associated with an increased risk of cardiovascular disease." Recent research has indeed confirmed that B_6 deficiency increases circulating homocysteine concentrations, which are associated with premature vascular disease (EVM/00/19), and that 20 mg/day vitamin B_6 supplementation is able to reverse this effect in vitamin B_6 deficient asthma patients.[16]

It is stated in the draft document under the heading 'Genetic Variations' that "No genetic variations which increase vulnerability to toxicity of vitamin B_6 have been identified." What the EMV has overlooked here is that there are genetic variations that increase vulnerability to deficiency of vitamin B_6, specifically, MTHFR 677C-T polymorphism. This genetic variation, affecting some 10-15% of the population, increases levels of homocysteine and risks of CHD by reducing the efficacy of a specific homocysteine lowering enzyme. Deficiency of co-factors, including B_6, involved in this metabolism result in further elevated homocysteine levels.[17] Supplementation of 50-100 mg vitamin B_6 daily can improve transulfuration of homocysteine, thus lowering circulating levels and the associated CHD risks. This route for the detoxification of homocysteine is especially important for those 10-15% of the population with the MTHFR polymorphism, rendering the methylation of homocysteine less efficient. For these people limiting B_6 to 10 mg may be unsafe by virtue of increasing their risk of heart attacks and strokes, both of which are strongly associated with raised homocysteine levels.

Sub-optimum Levels of B_6 Contribute to Pre-Menstrual Syndrome; 100 mg/day Supplementation Improves Symptoms

A review of nine randomized placebo controlled trials representing 940 patients with premenstrual syndrome examined the effectiveness of vitamin B_6 in the management of premenstrual syndrome. Results suggested that doses of vitamin B_6 up to 100 mg/day are likely to be of benefit in alleviating premenstrual symptoms.[18]

Vitamin B_6 Deficiency More Common in Women Using Oral Contraceptives; 40 mg/day Supplementation Eliminates Deficiency

Research has confirmed an impaired vitamin B_6 status in women using hormonal contraception, contributing to such symptoms as depression, anxiety, decrease of libido and impairment of glucose tolerance. Administration of 40 mg of vitamin B_6 daily not only restores normal biochemical values but also relieves the clinical symptoms in those vitamin B_6 deficient women taking oral contraceptive agents.[19]

Low B_6 Plasma Levels Found in Asthmatics, 100 mg/day B_6 Supplementation Dramatically Helps

In 15 adult patients with bronchial asthma, plasma and erythrocyte pyridoxal phosphate (PLP) concentrations were

significantly lower than in 16 controls. Oral supplementation of seven asthmatics with 100 mg/day pyridoxine resulted in a dramatic decrease in frequency and severity of wheezing or asthmatic attacks while taking the supplement.[20]

Vitamin B_6 Reduces Risk of Kidney Stones in Women

The relation between the intake of vitamin B_6 and the risk of symptomatic kidney stones were prospectively studied by Harvard Medical School researchers in a cohort of 85,557 women with no history of kidney stones. A high intake of vitamin B_6 was inversely associated with risk of stone formation. The study concluded "Doses of vitamin B_6 of 40 mg/day may reduce the risk of kidney stone formation in women."[21]

Conclusion

From the above evidence it can be seen that a restriction of B_6 to a SUL of just 10 mg/day would make optimum health beyond the reach for sizeable subgroups of the population with vitamin B_6 deficiency, raised homocysteine levels, the MTHFR 677C-T genetic variation, PMS, women using oral contraceptives, asthmatics, and those at higher risk of kidney stone development. There is no scientific justification for restricting free access to this essential nutrient with a long history of safe use in the dose range of 100-200 mg daily.

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