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Vitamin B6: "It's the Form, stupid"

Why regulators in the EU will increasingly find themselves in Court…. unless they take note of the clinical and scientific evidence

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Holland is set to pull off a memorable April Fool's Day trick next Spring that's no fool – it's for real. We're talking here about the limitation of all forms of vitamin B6 in food supplements to 21 mg per day. This may be over 3 times the new 6 mg/day maximum level for the vitamin set by neighbouring Belgium, which came into force last month (10th November). But the Netherlands has long been the bastion of liberal regulatory approaches to food supplements in the EU – and this decision, that has been in the making some time, marks a definite change in policy.

Putting these ludicrously low levels into perspective, the 100-mg level established as safe to all consumers in the USA by the US Institute of Medicine is nearly 5 times higher than the proposed Dutch level — and nearly 17 times that of Belgium. Botanical-liberal Italy doesn't feel the same way over vitamins and has a number of low maximums for supplements, including just 9.5 mg per day for B6, albeit a move in the right direction from its previous 6 mg maximum.

Germany is of course the archetypal restrictive EU Member State when it comes to micronutrients. Table 1 shows you the EU NRVs (the new name for RDAs, Recommended Daily [or Dietary in the US] Allowances – perhaps better described as the 'Ridiculous Dietary Arbitraries'!). It also shows the EU, UK and US 'upper levels' considered safe from all sources (i.e. conventional foods, fortified foods, supplements). It compares these with, in the extreme right-hand column, the maximum permitted levels allowed in supplements in Germany.

These maximum levels for supplements were developed by the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR) for vitamins in 2005 and for minerals in 2006. By example, the pitiful 9 µg (micrograms or mcg) per day maximum permitted level for vitamin B12 in supplements, which in reality have almost no upper threshold for safety, is a reminder over how the German authorities are abusing the concept of scientific risk assessment. This is the only mechanism regulators can use, according to case law set by the European Court of Justice (ECJ), to limit public access to food supplements that are not clearly medicinal by function or presentation.

Table 1. Reference and upper levels compared with maximum permitted levels for food supplements in Germany

MICRO-NUTRIENT	EU LEVELS OF ADEQUACY (Nutrient Reference Values) [NRVs]	UPPER LEVELS* FOR SAFETY [TULs] (Tolerable Upper Levels)			MAX SUPPLEMENT LEVEL GERMANY
Authority	EFSA	EFSA	EVM	IOM	BfR
VITAMINS					
Vitamin A (µg RE)	800	3000 (30,000IU from carotenoids, 9,990IU from retinol) (does not apply to	1500 (GL)	3000	400 (4,000IU from carotenoids, 1,332 from retinol) (only for adults)
Vitamin D (µg)	5	50 (2000IU)	25 (GL in addition to food)	100	5 (200IU)
Vitamin E (mg α-TE)	12	201 (300IU)	800IU (536 mg) (SUL in addition to food)	670 (1000IU)	15 (22.4IU)
Vitamin K (µg)	75	not set	1000 (GL in addition to food)	not set	80
Vitamin B1 (mg)	1.1	not set	100 (GL in addition to food)	not set	4
Vitamin B2 (mg)	1.4	not set	40 (GL in addition to food)	not set	4.5
Nicotinic acid (mg)	16 (mg NE)	10	17 (GL for supplements only)	35 (niacin)	0
Niacin (mg NE)	16	900	560 (GL)	35 (niacin)	17
Pantothenic acid (mg)	6	not set	200 (GL in addition to food)	not set	18
Vitamin B6 (mg)	1.4	25	10 (SUL in addition to food)	100	5.4
Folic acid (µg)	200	1000	1000(GL in addition to food)	1000	400 (as folic acid)
Vitamin B12 (µg)	2.5	not set	2000 (GL in addition to food)	not set	3-9
Biotin (µg)	50	not set	900 (GL in addition to food)	not set	180
Vitamin C (mg)	80	not set	1000 (GL in addition to food)	2000	225
MINERALS					
Calcium (mg)	800	2500	1500 (GL in addition to food)	2500	500
Magnesium (mg)	375	250 (for supplements only)	400 (GL in addition to food)	350	250
Iron (mg)	14	not set	17 (GL in addition to food)	45	0
Copper (µg)	1000	5000 (not applicable during pregnancy or	10,000 (SUL)	10,000	0
Iodine (µg)	150	600	500 (GL in addition to food)	1100	100
Zinc (mg)	10	25	25 (SUL in addition to food)	40	2.25
Manganese (mg)	2	not set	12.2 (GL)	11	0
Sodium (mg)	not set	not set	not set	not set	0
Potassium (mg)	2000	not set	3700 (GL in addition to food)	not set	500
Selenium (µg)	55	300	450 (SUL)	400	25-30
Chromium (µg)	40	not set	10,000 (GL)	not set	60
Molybdenum (µg)	50	600	not set	2000	80
Fluoride (mg)	3.5	7 (for children above 8yrs and adults)	not set	10	0
Chloride (mg)	800	not set	not set	not set	0
Phosphorus (mg)	700	not set	250 (GL in addition to food)	4000	250 (as Phosphate)
Boron (mg)	not set	not set	9.6 (SUL)	20	not set
Vanadium (mg)	not set	0.175 (2008 opinion)		1.8	not set
Silicon (mg)	not set	not set	1500 (SUL supplemental silica equiv. to 700mg of elemental silicon)	not set	not set

*Tolerable Upper Levels are determined by risk assessment of available data. The UK Expert Group on Vitamins and Minerals (EVM) has set Guidance Levels (GLs) where there are insufficient data to undertake full risk assessments.

What a load of B…

While the 5.4 mg level for vitamin B6 appears highly scientific, it's simply a crude (and we think deliberate) over-calculation of risk that's akin to telling motorists it's compulsory to wear a minimum of 4 seatbelts regardless of what motor vehicle they're driving.

The BfR takes the European Food Safety Authority (EFSA)'s already deeply questionable 25 mg upper level as its starting point that's 4 times lower than the US Institute of Medicine's 100 mg safety threshold for dietary supplements. The EFSA's level itself relies heavily on a discredited UK study by Dalton & Dalton (1987) on 172 menopausal women using the pyridoxine form of the vitamin, a fact acknowledged in the EFSA's opinion, as follows:

> This study has been severely criticised because of its design; all subjects received vitamin B6 and the comparisons were between those who did, and those who did not report adverse effects. The adverse effects may have predated treatment with B6. The only evidence for cause and effect relates to the consequence of stopping or not stopping intake, and correlations with duration of intake.

It's worth noting that none of the 172 women in Dalton & Dalton's discredited report had neurological examinations, the reported peripheral neuropathy being entirely self-reported. What's more, the 103 of 172 women with reported neurological symptoms were taking almost exactly the same dose (117 mg/day of the pyridoxine form of vitamin B6 on average) as those without any reported symptoms (116 mg/day of pyridoxine on average). There was however a difference in the duration of intake: on average nearly 3 years for the women reporting

symptoms, against just over 2 years for those without. All in all, considering the wealth of other evidence on pyridoxine, it is astonishing that this deeply flawed study has been used as evidence by EFSA and other European authorities and is then applied to all forms of the vitamin.

So how does the BfR get to its 5.4 mg maximum level for food supplements? It just takes 5 simple, over-precautionary, disproportionate steps. This is how it goes: armed with this very low, Dalton & Dalton-influenced upper level, the BfR then subtracts the highest amount that it has found consumers ingesting from foods in the normal diet based on German intake studies. This number is 3.43 mg/day. Take this away from EFSA's 25 mg and you get left with a residual amount of additional intake of vitamin B6 from food supplements of 21.57mg.

Rather than leaving it like this – which, incidentally, is the rationale used by the Dutch authorities, the Germans have applied a further two 'safety factors' (additional seatbelts). The first of these takes into account the possibility that German consumers might already be consuming half of their residual intake from fortified foods, leaving only 50% of the residual amount for food supplements. In short, that means dividing by 2.

If that wasn't enough, the final Germanic 'safety' factor to be dialled in is the so-called 'multiple exposure factor' which considers the possibility that people might take two supplements in a day containing vitamin B6. That means dividing by 2 – again! The authorities appear to distrust the public's ability to keep a tab on their own intake – making something of a mockery of the mandatory Nutritional Information panels on the back of supplement packages. Such assumptions are frankly slights against consumer awareness and intelligence, let alone, when turned into law, a great injustice to fundamental rights and freedoms.

For those who are more visual, following is a summary of the 5 steps in BfR's calculation:

STEP 1. 25 mg – starting point, EFSA's faulty 25 mg Tolerable Upper Level
STEP 2. 3.43 mg – the highest percentile daily intake in the German population
STEP 3. 25 minus 3.43 = 21.57 mg for residual intake over and above the normal diet
STEP 4. 21.57 / 2 = 10.785 mg which represents the amount to be split equally (with no adequate scientific justification) between food supplements and fortified foods
STEP 5. 10.785 / 2 = 5.4 mg this further halving taking into account Germans might unknowingly consume two supplements in a day (with no evidential basis)

What's wrong with the BfR's calculation?

Many things. Here are a few major problems:

- It relies on the EFSA Tolerable Upper Level (TUL) that is misapplied to the pyridoxal and pyridoxamine forms of vitamin B6, when the adverse effect on which it is based is limited to the pyridoxine forms (Figure 1) which is in turn greatly influenced by a faulty study. For generalised scientific problems with the setting of TULs, refer to our 2010 review published in the peer-reviewed journal *Toxicology*.
- It assumes supplement consumers are consuming half their additional intake over and above normal foods from fortified foods, when no fortified foods we can find on the German market contain anything like 10.785 mg of vitamin B6.

- It assumes that the bioavailability of all forms of vitamin B6 in the diet or in supplements is the same, when it is known that the forms commonly found in plant foods are generally glycolysated (bound) and have significantly lower bioavailability, hence adversely affecting vitamin B6 status.
- It assumes that consumers are not able to make informed decisions about their daily intake of nutrients from multiple sources or supplements.
- It entirely ignores any benefits that might be derived at levels higher than the amounts required for mere nutritional adequacy (i.e. the NRV). The paradox of overlapping risks and benefits was the subject of another paper I had published in *Toxicology* in 2010.
- The over-cautionary approach associated with pyridoxine overdose being linked to peripheral neuropathy has made both health professionals and significant numbers of the public blind over the usefulness of vitamin B6, as pyridoxine or pyridoxal, as a well-established treatment for drug-induced (e.g. isoniazid) peripheral neuropathy. In menopausal women, the requirements for B6 can often also be higher than at other life stages, and they may be consumed primarily as glycosylated forms in the diet (from plants) with low bioavailability, contributing to low B6 status.
- Finally, the approach used by the BfR assumes all forms of vitamin B6 have the same risks on the body. In the EU, only three forms are allowed: two forms are based on pyridoxine (the hydrochloride and phosphate forms), while the third is the active coenzyme form, pyridoxal-5'-phosphate, also known as P5P or PLP (Figure 1). Crucially, peripheral neuropathy has never been associated with this latter coenzyme form.

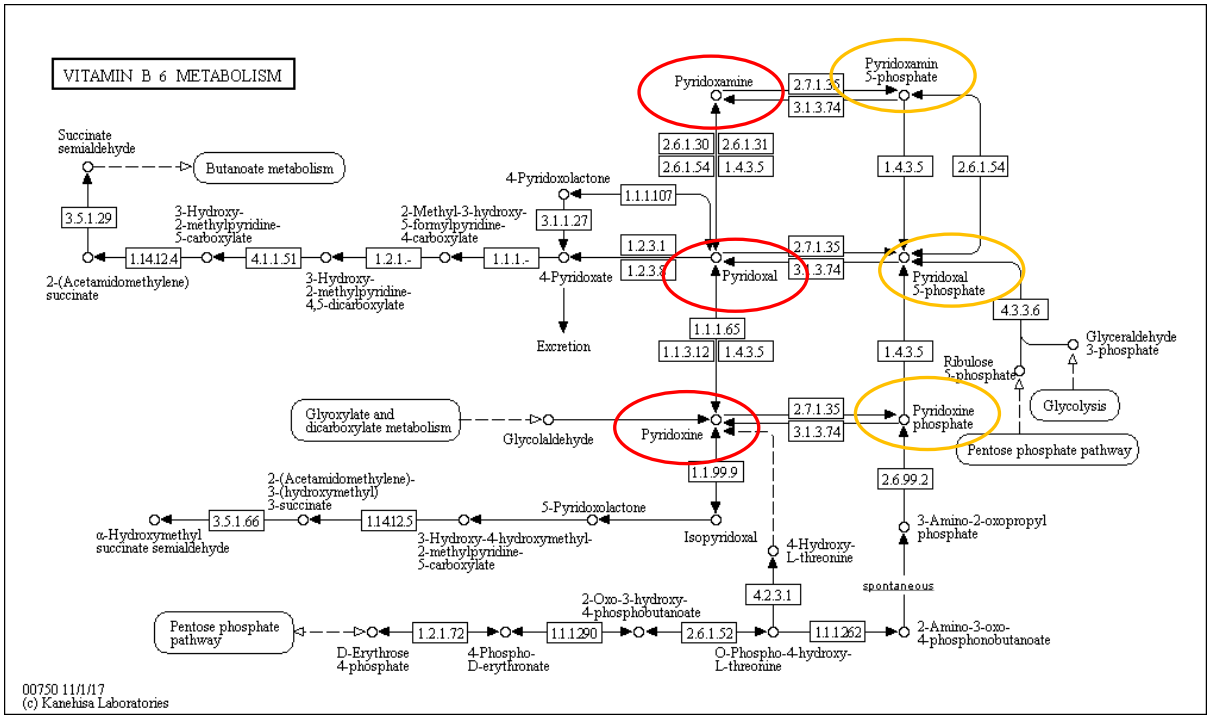

Figure 1. Metabolism of vitamin B6 (Courtesy: Kegg pathways, vitamin B6 reference pathway, Kanehisa Laboratories). Red ovals denote the key vitamin B6 vitamers, the orange ovals their phosphate forms. Pyridoxal 5'-phosphate is the metabolically active form of the vitamin.

What's the F…?

F stands for form, in case you thought otherwise. So here, let us take up the final bullet point above.

Regulators in Germany, Belgium, Holland and Italy are not alone in their concerns over the long-term use of high dose vitamin B6 in the pyridoxine form. American regulators in the FDA have similar concerns. But it depends what you mean by 'high dose' and whether in referring to 'high dose' it is expected that adverse effects, notably peripheral neuropathy, are a possibility or likelihood. Doses of 25, 50, 100 or 200 mg may be considered high dose in that they are significantly higher than the amounts that can be typically achieved from the normal diet. But they are not generally associated with neuropathic risk (unless you believe Dalton & Dalton's discredited work). These amounts, and in some cases up to 500 mg/day of vitamin B6 are often exactly what is required to sort out energy, endocrine and nervous system/neurotransmitter metabolism in significant numbers of people, especially peri-menopausal and menopausal women.

Peripheral neuropathy, a tingling, numbness or pain sensation in the extremities, is the adverse effect that regulation of B6 doses aims to protect us from. It's an increasingly common problem, and is particularly common among diabetics, cancer patients treated with neurotoxic chemotherapy, HIV patients treated with antiretroviral drugs and those suffering heavy metal toxicity or vitamin B6 deficiency. Yes, that's right, the same adverse effect can be caused by too little or too much vitamin B6. Remember this point, as it's of seminal importance, as you'll discover later in this article.

The exhaustive review of animal and human clinical studies on the use of vitamin B6 by Adrianne Bendich and Marvin Cohen in 1990 (*Ann N Y Acad Sci* 1990; 585: 321-30) is a sound reminder of the anomalous findings by Dalton & Dalton that UK and EU authorities have used with such aplomb to limit levels of the vitamin. Bendich and Cohen show from multiple studies, extremely high doses of 1000 mg pyrodoxine/day generally yield a degree of peripheral neuropathy after a few months of use, while levels of 500 mg/day do so in a small number of people but usually only with long-term use (a number of years). Moreover, at 200 mg/day, no one (other than the misreporting in the Dalton & Dalton study) is reported as suffering any peripheral neuropathy.

Two incredibly important points emerge from all of this; one is linked to the form used, the other to the benefits gained by the user:

> **Form:** Given the association between high-dose pyridoxine and the potential risk of peripheral neuropathy, women are increasingly opting to take the active form of vitamin B6, pyridoxal-5'-phosphate (P5P), rather than pyridoxine. P5P is a coenzyme required for numerous key functions in the body, including in amino acid, carbohydrate and lipid metabolism, including pathways involving energy-yielding metabolism and neurotransmitter function. This breadth of roles of the vitamin is an important reason why it has such profound effects on energy levels as well as on mood. Crucially, there is not a single published report on P5P causing peripheral neuropathy – the sole form for which neuropathic symptoms have been reported are the various forms of pyridoxine.
>
> It is fitting, just as the Dutch government is planning to limit vitamin B6, a study just published by researchers from the Department of Pharmacology and Toxicology at Maastricht University sheds light on the mechanism of action of pyrodixine based on *in vitro* cell studies. What the researchers have shown is that high dose pyridoxine

competitively inhibits the active form P5P thus yielding neuropathic symptoms that are identical to vitamin B6 deficiency. As importantly, the researchers found no dose-related adverse effects on cell viability were noted for the other forms of vitamin B6 tested, notably pyridoxamine, pyridoxal, pyridoxal-5'-phosphate and pyridoxamine-5'-phosphate.

This means, for the first time, we have scientific evidence for why all the risks, as established from thousands of clinical cases in which high dose vitamin B6 cases have been evaluated, are related to the pyridoxine forms, and not to the pyridoxal forms.

Benefits: People use high doses of vitamins to yield benefits. Members of the public who experience benefits communicate this to others, as seen in this example posted on a form on the Patient website. Regulators choose to either consider risk completely in the absence of benefit, because they are tasked with risk assessment, not risk/benefit assessment. Or they use the profound physiological functions to justify its medicinal status. It's not hard to see why regulators and the drug industry have long wanted to limit high-dose vitamin B6, given its diverse range of clinical uses, as summarised by Bendich and Cohen, include the following:

> Autism, Down's syndrome, infantile convulsions (dependency), migraine headaches, schizophrenia, alcoholism withdrawal, seizures, antagonism of drugs (isoniazid, levo-dopa) or natural products (mushroom poisoning), carpal tunnel syndrome, diabetic complications, preeclampsic edema, premenstrual syndrome, homocystinuria, hyperoxaluria, xanthinuric aciduria, asthma, radiation sickness and sickle cell anaemia.

Missing from this list is of course the very reason Dalton & Dalton were using vitamin B6, with or without other B vitamins (notably folate and B12) and minerals (notably magnesium): peri-menopause and menopausal mood swings, anxiety, depression and fatigue. The benefits among women taking 100 – 300 mg vitamin B6 per day can be profound.

Court cases in the EU – and your support

There are presently six cases awaiting judgment in various levels of the Swedish courts in relation to vitamin B6 food supplements containing dosages over 25 mg.

We are presently endeavouring to commission the TNO in The Netherlands to conduct a risk/benefit assessment of vitamin B6 as a means of providing additional evidence in support of these cases. We have been raising funds for this work for several months and are hopeful that we will soon have the required funding to commission the work. Further funding is required to have the work published, which will have greater impact, not only in Europe, but internationally.

Any parties interested in donating to support this work should contact us at info@anhinternational.org with the subject 'Vitamin B6 risk/benefit'. We are also hoping to outsource PR to publicise more widely the issues around disproportionate restrictions on vitamin B6, especially in relation to the pyridoxal forms.

The European Court of Justice (ECJ) has frequently referenced, in its judgments relating to food supplement restrictions, that restriction of the free movement of foods in the EU can only be made on the basis of the latest risk assessment. We are working to ensure this risk/benefit work

has to be considered. Any restriction in the face of it would be disproportionate and therefore capable of legal challenge. That's why we suggested in the teaser to this piece that regulators, if they don't take note of the science on vitamin B6 and its forms, will likely increasingly find themselves in court.

Please share this article widely. It may be republished on other websites on the condition that the source is clearly indicated.

Acknowledgement

I would like to thank a practitioner and friend in Sweden for his suggestion for this article's title. He is closely involved in the Swedish cases defending the use of doses of vitamin B6, including in the P5P form over 25 mg/day, and in a recent conversation he made mention of the parallel between the issue of doses for botanicals and forms for vitamins. Back in 2009, lawyers Sebastián Romero Melchor and Liesbeth Timmermans published a seminal piece in the journal *European Food and Feed Law Review* that has been critical to public, industry and regulator understanding of the complexities between the food/medicine borderline in relation to botanicals as deliberated by the ECJ. The article was entitled *"It's the Dosage, stupid": The ECJ clarifies the Border between Medicines and Botanical Food Supplements.* You'll now appreciate why we've given this piece the title *"It's the Form, stupid*".