

Supplements (Part 1): Vitamins

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Introduction

Several incidents occurring in quick succession prompted the exploration of this topic.

First was the commencement of the Medicines and Related Substances Control Amendment Act, (1997 and 2002), of the Medicines and Related Substances Control Act 101 of 1965, which came into effect on 2 May, 2003.¹

Next was the suspension by the Australian Therapeutic Goods Administration (TGA) of Pan Pharmaceuticals Limited's manufacturing licence for six months.² Pan Pharmaceuticals is said to be Australia's leading manufacturer of complementary medicines.³ (*SA Fam Pract* 2003;45(5): 18-23)

As is stated on the TGA website:²

'The Therapeutic Goods Administration (TGA) has suspended the licence held by Pan Pharmaceuticals Limited of Sydney to manufacture medicines, for a period of six months with effect 28 April 2003, because of serious concerns about the quality and safety of products manufactured by the company.

The suspension follows audits of the company's manufacturing premises, which revealed widespread and serious deficiencies and failures in the company's manufacturing and quality control procedures, including the systematic and deliberate manipulation of quality control test data.

The licence has been suspended in order to urgently address the safety and quality concerns posed by the multiple manufacturing breaches. ***Where the quality of a medicine cannot be certain, neither can the safety or effectiveness of that medicine.***

Due to the serious and widespread nature of the manufacturing problems identified and following expert advice regarding potential risks, the TGA has taken the decision to recall all batches of medicines manufactured by Pan Pharmaceuticals Ltd since 1 May 2002 and that are being supplied on the Australian market.

Two hundred and nineteen products manufactured and supplied in Australia by Pan Pharmaceuticals Limited have

been identified for immediate recall. These products have been cancelled from the Australian Register of Therapeutic Goods for quality and safety reasons. The company has also had its approval to supply its range of export products (approximately 1650) cancelled.'

Apparently some of these export products come to South Africa and this is being followed up by the authorities. Section 26 of the new Act which deals with the roles and powers of the inspectorate of our Medicine's Regulatory Affairs (MRA) only comes into effect on 1 July 2005. It is unlikely that the kind of extensive audits undertaken by the TGA will take place in South Africa until well after that date. This does not mean that the inspectorate is unaware of these kinds of problems or unable to act, and within their statutory and logistical constraints they are acting wherever possible.

The following 'incident' was the publication by the UK 'Expert Group on Vitamins and Minerals' (EVM) of their final report in May 2003 titled: Safe Upper Levels for Vitamins and Minerals.⁴ This is the outcome of a four year deliberation and consultation, which commenced in January 1999. In my opinion this report is comparable in importance to the seminal United States Preventive Services Task Force reports.⁵

The final incidents which attracted

my attention were two instances of the random awarding of hampers containing supplements and herbal substances as prizes on different radio stations. One of the promoters of such products was interviewed and recommended taking high doses of supplements, stating that 'RDAs could be ignored' or words to that effect.⁶

The press release distributed by the UK Food Standards Agency (FSA) subsequent to the release of the EVM report indicates that:⁷

- Chromium in the form of chromium picolinate may have the potential to cause cancer; consumers are advised not to take chromium in this form. The FSA has consulted on a proposal to ban its use in the manufacture of food supplements. Having 10mg/day or less in total of chromium in **other** forms is unlikely to cause any harm. [my emphasis]
- Levels of vitamin C above 1000mg/day could cause abdominal pain and diarrhoea. Similarly, high intakes of calcium (above 1500mg/day) and iron (above 17mg/day) may result in similar symptoms in some people. These symptoms should disappear once people stop taking the supplements.
- There are some substances that may have **irreversible** harmful effects if taken for long periods at the highest supplemental doses. These include

beta-carotene (especially for smokers and those exposed to asbestos), nicotinic acid, zinc, manganese (especially for older people) and phosphorus. [my emphasis]

- Current advice on vitamin B6 is being re-emphasised. The Agency advises against taking more than 10mg/day of vitamin B6 from dietary supplements unless acting on medical advice. High intakes taken over a long period of time can lead to paraesthesiae.

In my opinion it is irresponsible to indiscriminately promote taking supplements. However, it probably reinforces widely held beliefs about supplements and also reflects the widespread practice of manipulating (mainly through advertising) the thinking of the general public in terms of what is, and what is not, required for good health.

The supposed rationale for the average person needing supplements at all, is that most people do not have healthy, balanced diets. Even those who do eat 'properly' the argument is that their food is so contaminated with pollutants, pesticides, antibiotics and hormones that it is not providing all the nutrients the human body requires to function properly.

There may well be elements of truth in some of this. But to advocate that the 'antidote' is to substitute food with artificially produced pills, tablets, capsules and powders, is certainly misleading. In contrast, there is research involving certain P-glycoproteins (e.g. gp170) which actively remove so-called 'toxins' at a cellular level. This is one of the hypothesised mechanisms for the development of drug resistance with the use of certain anti-tumour ('chemotherapy') agents, and even against some antibiotics.^{8,9} This does not apply, of course, to frankly poisonous, sometimes lethal substances.

In terms of supplements, it is important to note that the definition of a medicine according to the amended Act has not changed. It is:

any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in –
a. the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or

mental state or the symptoms thereof in man; or

- b. restoring, correcting or modifying any somatic or psychic or organic function in man, and includes veterinary medicine.¹*

The line between a supplement being i) a 'nutritional complement' to the average person's supposedly inadequate diet, and being ii) a medicinal substance, is tenuous at best and misleading at worst.

Several questions need to be asked. Is there a legitimate point when the average person could start using a supplement as a medicine? Would this not form part of the move towards increasing 'self care' and 'self responsibility' particularly favoured by medical aids at present? Isn't this what health promotion and 'wellness' are all about? (There is now even a 'Wellness Programme' for dogs involving nothing more than the addition of a nutritional 'gravy' to their pellets!) To what extent should the lay person be self-diagnosing and self-treating in terms of using supplements? What are the advantages of this? Are there inherent dangers? (See comments on kava kava in a previous edition of SA Family Practice/Geneeskunde.¹¹)

It is interesting to note that parallel to public concerns expressed about antibiotics in foods, the public have recently been inundated with antimicrobial-containing soaps and detergents. Very little opposition to these products has (as yet) been voiced in South Africa. Some concerns about these substances creating resistant micro-organisms have however been expressed.¹⁰

Nearly every claim I've seen made for supplements, particularly in advertisements, would lead to them being classified as a medicine according to the definition in the Act.¹ However supplements are not registered medicines – which means that neither their quality, safety, nor efficacy have been rigorously assessed. Just one of the possible reasons for the quality problems picked up by the TGA is that manufacturers of vitamins and minerals deliberately

increase the amounts of some of the components which deteriorate over time, so as to ensure their shelf life. This is known as 'overage'. What it means is that when purchasing newly manufactured supplements, the consumer may in fact be getting an overdose of certain components.⁴ It is not clear to what extent this happens in South Africa, but because these products are not fully regulated, there is presently no obligation on the part of manufacturers (apart from a moral one) to ensure that the quality of their products remain constant and consistent. As pointed out above, if the quality is not assured, neither can the safety or the efficacy be assured. One could argue that the shelf life should be decreased rather than the amounts contained in the supplements increased – this however would most likely not make the products competitive in terms of price or profits.

Only a fraction of the information available can be presented in articles of this nature, and it has become necessary to make this a two-part article. Part 1 will focus on Vitamins; Part 2 will focus on trace elements and minerals. Other 'supplements' such as the essential fatty acids will not be included in these brief reviews. The antioxidant properties of various substances is mentioned where relevant.

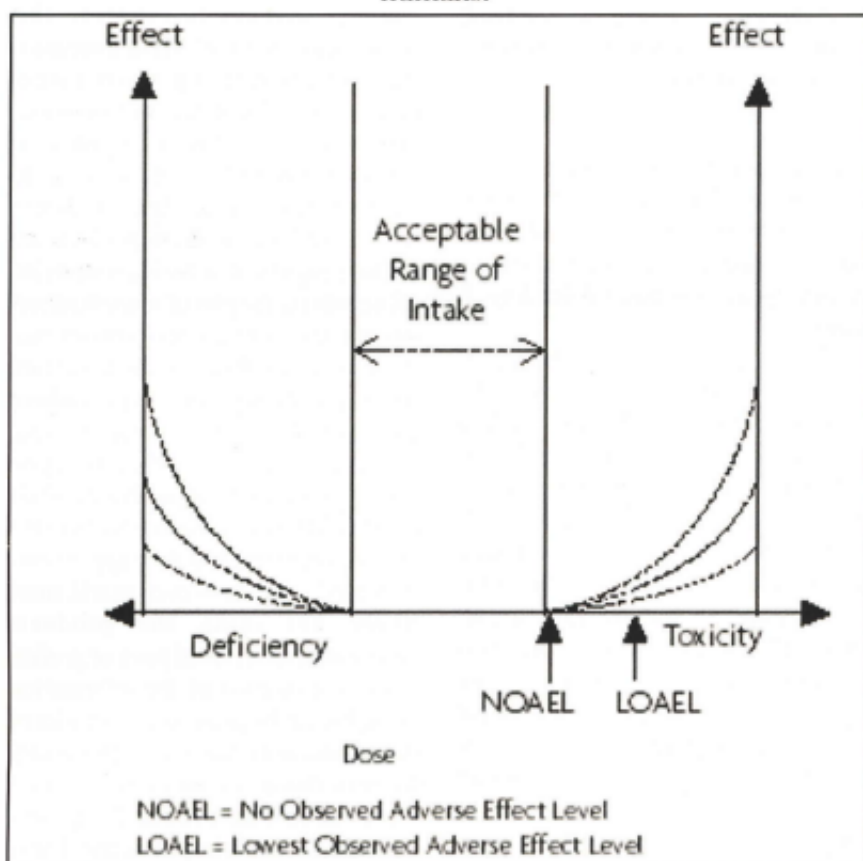
SAFE UPPER LEVELS

Nutrients are essential for human health. Clearly the range of nutrient-intake can, simplistically, be from 'too little' to 'too much'. Too little results in the deficiencies of which most medical doctors remain aware – even if only as a distant memory from medical school days. Too much may result in toxicity, and the EVM report details many of the vitamins and minerals which are toxic in excess. This range is portrayed in Figure 1.⁴

The EVM made it clear that their recommendations did not address the medicinal uses of vitamins and minerals (i.e. 'efficacy') as their mandate was to consider only the nutritional aspects.⁴ However, where applicable, the report does provide information about deficiencies, drug interactions, and toxic effects of excessive doses.

According to the EVM, 'the

Figure 1: Theoretical nutrient dose-response relationships in humans.⁴



determination of Safe Upper Levels (SULs) or Guidance Levels entails the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provides a framework within which the consumer can make an informed decision about intake, having confidence that harm should not ensue.⁷⁴ However because, for the majority of vitamins and minerals, the available database is inadequate to establish Safe Upper Levels, guidance has been given on the levels that would not be expected to be associated with adverse effects. It is acknowledged that such Guidance Levels may not be applicable to all life stages or for life-long intake. These latter determinations have been called 'Guidance Upper Levels' in the tables below.

The 360 page report provides all the details on how the expert committee's conclusions were reached including all the references. The report is a good example of both the limitations and the

advantages of applying evidence-based conclusions. [Note: Although the report is well worth downloading and reading, it is a large 'pdf' file of 1.4 megabytes]

SPECIFIC CONSIDERATIONS

Tables I and II have been constructed from the EVM report, focusing primarily on interactions and toxicity of vitamins, as these could have practical implications for general practitioners and family physicians in South Africa. The vitamins are listed in the order in which they appear in the report. Where applicable the proposed new Recommended Dietary Allowances (RDAs) under the apparently yet to be promulgated Regulations have been included,¹² and compared to the 'old' values.¹³ The EVM upper level guideline is also incorporated or where these have been specified, the 'safe upper level'.⁴

Note that Vitamin C is a 'pro-oxidant' (the opposite of an antioxidant) at very high doses, a fact worth pointing out to some patients who may think that

'more is better'.

Note the level of Vitamin A at which teratogenicity may develop.

Note the increased chances of developing lung cancer in smokers and asbestos-exposed individuals receiving β -carotene.

COENZYME Q10

A substance being widely promoted and included in many 'supplements' is coenzyme Q10. Coenzyme Q10 (also known as Co Q10, Q10, vitamin Q10, ubiquinone, or ubidecarenone) is a benzoquinone compound primarily synthesized by the human body,¹⁴ and is an *endogenous antioxidant*.¹⁵ (my emphasis) It is important to point out to patients and the general public that the body can make its own antioxidants. No coenzyme Q10 deficiency symptoms have been reported in the general population, so it is generally assumed that normal biosynthesis and a varied diet provides sufficient coenzyme Q10 for healthy individuals.¹⁴ Comment: There is clearly no need to take in additional coenzyme Q10 in the form of supplements. (A particularly spurious and unscrupulous, in my opinion, form of public deceit has recently emerged. Patients are encouraged to take prepackaged over-the-counter 'supplements' to counteract the 'depleting' effects of the medications they are on. One of the common ingredients is coenzyme Q10, which is made by the body, and could just as easily be supplemented – if necessary – by eating just about anything.)

Coenzyme Q10 is present in most tissues, but the highest concentrations are found in the heart, the liver, the kidneys, and the pancreas. The lowest concentration is found in the lungs.¹⁵ Rich sources of dietary coenzyme Q10 include mainly meat, poultry, and fish. Other relatively rich sources include soybean and canola oils, and nuts. Fruits, vegetables, eggs, and dairy products are moderate sources of coenzyme Q10. It has been estimated that dietary consumption contributes about 25% of *plasma* coenzyme Q10. The extent to which dietary consumption contributes to *tissue* coenzyme Q levels is not clear.¹⁴ (my emphasis)

Some patients using coenzyme Q10

Table I: Water Soluble Vitamins

Nutrient	Drug Interaction ⁴	Toxicity ⁴	Proposed RDA ¹²	'Old' RDA ¹³	EVM ⁴
Biotin	certain anticonvulsants, alcohol, steroid hormones	none reported.	0.03 mg	0.1 mg	GUL*: 0.9 mg
Folic Acid	anti-folate drugs, some anticonvulsants, some anti-inflammatories, zinc?	'indirect toxicity' = masking of vitamin B12 deficiency neuropathy, hypersensitivity	0.4 mg	0.2 mg	GUL*: 1 mg
Niacin / Nicotinic acid / Nicotinamide (Vitamin B3)	isoniazid, clonidine, ganglion-blockers	flushing, itching of the skin, nausea, vomiting and gastrointestinal disturbances, jaundice, hyperglycaemia, abdominal pain, elevated serum bilirubin, alkaline phosphatase and aminotransferase levels.	18 mg	18 mg	GUL*: 17 mg†
Pantothenic acid	vitamin C some B vitamins biotin	possible diarrhoea and gastrointestinal disturbances; possible increases in serum aspartate transaminase levels.	5 mg	6 mg	GUL*: 200 mg
Riboflavin (Vitamin B2)	iron, zinc and calcium; streptomycin; erythromycin, tyrothricin, carbomycin and tetracyclines; thyroid hormones, corticotrophin and aldosterone; phenothiazines and possibly tricyclic antidepressants; boric acid; probenecid	harmless yellow discoloration of urine; possible dermatitis	1.6 mg	1.6 mg	GUL*: 40 mg
Thiamin (Vitamin B1)	alcohol, acetylcholine antagonists, 5-fluorouracil	headache, nausea, irritability, insomnia, rapid pulse and weakness.	1.4 mg	1.4 mg	GUL*: 100 mg
Pyridoxine (Vitamin B6)	riboflavin, zinc and magnesium, levodopa, isoniazid, phenytoin, theophylline and phenobarbitone, oral contraceptives?	paraesthesiae, drowsiness, low serum folic acid levels, stumbling gait, perioral numbness, night restlessness, vivid dreams, sun sensitivity and an acne-like rash	2 mg	2 mg	SUL‡: 10 mg
Cyanocobalamin (Vitamin B12)	prednisone, alcohol, vitamin C, chloramphenicol	possible allergic reactions	0.003 mg	0.001mg	GUL*: 2 mg
Ascorbic acid (Vitamin C)	absorption of metal ions may be altered (e.g. increases uptake of iron)	gastrointestinal effects, metabolic acidosis, changes in prothrombin activity, 'conditioned need' scurvy, claims of renal stones, renal tubular disease and oxaluria, pro-oxidant at very high concentrations.	75 mg	60 mg	GUL*: 1000mg

*GUL: the supplementary intake per day in a 60 kg adult that would not be expected to be associated with adverse effects

† excluding sustained release preparations

‡SUL: Safe Upper Level for daily supplementary intake in a 60 kg adult over a lifetime

Table II: Fat Soluble Vitamins

Nutrient	Drug Interaction ⁴	Toxicity ⁴	Proposed RDA ¹²	'Old' RDA ¹³	EVM ⁴
Retinoids (Vitamin A [‡])	tetracycline, minocycline, ketoconazole, decrease vitamin C tissue storage, vitamin K, iron, alcohol (zinc)	<i>Acute:</i> abdominal pain, anorexia, vomiting, blurred vision, irritability, headache, bulging of fontanelles <i>Chronic:</i> dryness and thickening of the skin, cracking of lips, conjunctivitis, erythematous eruption, alopecia, reduced bone mineral density, bone joint pain, chronic headache, intracranial hypertension, hepatotoxicity	0.8 mg RE	1 mg RE	No GUL* or SUL† but total daily intake >1.5 mg RE 'inappropriate' NB: 3 mg RE is threshold for teratogenicity§
β-Carotene [°]	other carotenoids (e.g. lycopene, lutein and canthaxanthin)	reversible yellowing of the skin (hypercarotenodermia), association of high dose β-carotene supplementation (20-30 mg/day) with increased incidence of lung cancer in smokers and asbestos-exposed individuals	not specified	not specified	SUL†: 7 mg
Vitamin D	actinomycin, imidazole, lead, some anticonvulsants	hypercalcaemia, hypercalcuria,	0.006 mg¶	0.005 mg¶	GUL*: 0.025 mg¶
Vitamin E	vitamin A absorption	antagonises vitamins A, D, K, headache, fatigue, nausea, double vision, muscle weakness, mild creatinuria, gastro-intestinal distress, breast pain, dizziness, anti-platelet, anti-coagulant effects, possible increased risk of mortality from haemorrhagic stroke (under review)	15 mg** <i>d-α-tocopherol equivalents</i>	10 mg** <i>d-α-tocopherol equivalents</i>	SUL†: 540 mg** <i>d-α-tocopherol equivalents</i>
Vitamin K	vitamin E, vitamin A, coumarin anticoagulants actinomycin D	oxidative damage, red cell fragility, formation of methaemoglobin, (hyperbilirubinaemia, kernicterus in premature infants††), local hypersensitivity reactions	not specified	not specified	GUL*: 1 mg‡‡

* GUL: the supplementary intake per day in a 60 kg adult that would not be expected to be associated with adverse effects

† SUL: Safe Upper Level for daily supplementary intake in a 60 kg adult over a lifetime

‡ Acute vitamin A toxicity in humans is rare, but is more likely to occur following ingestion of high dose supplements, rather than following high intakes of vitamin A from food. Vitamin A accumulates in the body and, therefore, individuals who have regular high daily intakes of vitamin A might suffer adverse effects from chronic hypervitaminosis A. Although most manifestations of chronic vitamin A toxicity are reversible on cessation of dose, permanent damage to liver, bone and vision, and chronic muscular and skeletal pain may occur in some cases.

§ does not recommend Vit A supplements in pregnancy or in those who wish to become pregnant.

° β-Carotene is not classed as an essential vitamin, but it is a provitamin of vitamin A.

¶ 0.001 mg cholecalciferol = 40 I.U. Vitamin D

** 1 mg *d-α-tocopherol equivalent* = 1.49 I.U. (540 mg is equivalent to 800 I.U.)

†† High doses of water-soluble vitamin K3 (menadione)

‡‡ Use of menadione in food supplements is undesirable.

have experienced mild insomnia, elevated levels of liver enzymes, rashes, nausea, and upper abdominal pain. Other reported side effects have included dizziness, visual sensitivity to light, irritability, headache, heartburn, and fatigue.¹⁶

Drug Interactions:¹⁴

Warfarin:

Coenzyme Q10 decreases the anticoagulant effect of warfarin.

HMG-CoA reductase inhibitors

(statins):

HMG-CoA reductase inhibitors, may decrease the endogenous synthesis of coenzyme Q10.

Insulin:¹⁵

Coenzyme Q10 can decrease insulin requirements in individuals with diabetes. This may well be a worthwhile area of research, but indiscriminate intake may wreak havoc in diabetic control and result in possible overdoses of insulin. Diabetic patients need to be warned about and very careful of supplements affecting their ability to control their insulin needs.

Possible roles for coenzyme Q10 supplementation in cardiovascular diseases, neurodegenerative diseases, cancer, and diabetes require further research.¹⁴

CONCLUSION:

The widespread use of vitamin and mineral supplements has virtually become a dogma in today's society. The ability to isolate various ingredients into forms such as tablets and capsules in which they can easily and efficiently be taken in doses usually much higher than needed has been facilitated by modern pharmaceutical techniques. Often misleading and inaccurate advertising has contributed to this modern day mythology. Let us not, as medical practitioners, propagate this doctrine. □

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The South African Medical Devices Industry Association

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We are the representative association of the medical device and technology industry. Our mission is to safeguard and promote the interests of our members. We encourage ethical principles and practices and ensure effective representation with all relevant authorities whether public or private. SAMED focuses on health-care matters in South Africa where they affect our member's interests.

SAMED is committed to your needs

- We focus on creating a favorable environment for the profitable growth of our industry.
- We support the principle of a free market economic system which ensures job creation and meeting the needs of the population.
- We are committed to ongoing development of SAMED so that as an association we can effectively promote the objectives of our members.
- SAMED ensures that we work with the authorities so that standards and regulatory requirements are fair and practical.
- We believe in developing and maintaining fair employment practices within member companies.

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