Supplements (Part 2): Trace Elements, Minerals, Free Radicals and Antioxidants

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Introduction

These two articles are based mainly on the May 2003 report of the UK 'Expert Group on Vitamins and Minerals' (EVM) titled: Safe Upper Levels for Vitamins and Minerals.[1] This four year deliberation and consultation, which commenced in January 1999, used an evidence-based approach in providing information related to the use of supplements. Essential fatty acids were not included and neither have they been considered in these articles. In terms of the information about vitamins, trace elements and minerals presented in the articles, the emphasis has been on interactions with medicinal and other substances, as well as recorded adverse effects. Fluoride and sodium were not included, but the reviews are available. Sulphur, obtained mainly from the ingestion of amino acids, was also not included. *(SA Fam Pract 2003;45(7):60-64)*

The brief overview of free radicals and antioxidants included below can not be considered comprehensive but should provide sufficient information for a practitioner to explain some of the issues involved to her/his patient.

A reminder: The press release distributed by the UK Food Standards Agency (FSA) subsequent to the release of the EVM report stated that:[2]

- 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.
- 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.
- 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.

SPECIFIC CONSIDERATIONS

Tables I and II have been constructed from the EVM report. Where applicable the proposed new Recommended Dietary Allowances (RDAs) under the apparently yet to be promulgated Regulations have been included,[3] and compared to the 'old' values.[4] The EVM upper level guideline is also incorporated or where these have been specified, the 'safe upper level'.[1] According to the EVM, 'the determination of Safe Upper Levels (SULs) or Guidance Levels entails the determination of doses of vitamins and minerals [for a 60 kg adult] 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.'[1] A comparison between the amounts suggested by the EVM, and the amounts contained in a selection of the products available in South Africa could form the basis of a very useful research project.

Note that germanium is considered too toxic to be included in supplements and has been withdrawn from the UK supplements market. At least one product containing germanium was traced in South Africa by the author.[5] There is no indication whether or not this is 'organic' or 'inorganic' germanium, as 'organic germanium present in *food* does not appear to be associated with any adverse effects'.[1] (my emphasis) This product also contains strontium, which is not even considered in the EVM report. Vanadium is not an essential trace element, yet it is included in another South African product, with the claim that it aids the imbalance in glucose metabolism in hyperactive

Table I: Trace elements					
Substance	**Interaction**[1]	**Adverse Effects**[1]	**Proposed RDA**[3]	**'Old' RDA**[4]	**EVM**[1]
Boron	Calcium	acute lethal dose (boric acid) 3000-6000 mg forinfants; 15000-20000 mg in adults; irritability, seizures, gastrointestinal disturbances, possible decrease in sperm quality	None specified	None specified	SUL*: 9.6 mg
Chromium‡ (trivalent) [hexavalent form not recommended]	Iron – affects transferrin binding, impairs metabolism and storage	*Acute*: death by cardiogenic and renal shock, pancreatitis, haemorrhage and gut mucosal necrosis. *Chronic*: reversible anaemia, haemolysis and liver and renal dysfunction	None specified	None specified	GUL†: 10 mg
Cobalt§	Alcohol – can lead to cardiomyopathy, Iodine – uptake reduced	*Acute*: gastrointestinal upset, skin rashes, hot flushes; *Chronic*: effects on the heart, thyroid and possibly kidney	Not recommended	Not recommended	GUL†: 0.25 mg
Copper	Zinc, Iron, Vitamin C	intravascular haemolysis, acute hepatic failure, acute tubular renal failure, shock, coma or death if ≥100g ingested *Acute*: salivation, epigastric pain, nausea, vomiting, diarrhoea [Wilson's Disease]	Not specified	Not specified	SUL*: 10 mg
Germanium¶ (not an *essential* trace element)	Silicon, loop diuretics, inhibits activities of lactate and alcohol dehydrogenase, inhibits detoxication enzyme glutathione-S-transferase	*Cumulative*: initial anorexia, weight loss, fatigue and muscle weakness; followed by irreversible renal damage, dysfunction and failure which can be fatal; peripheral neuropathy	Not recommended	Not recommended	Not recommended
Iodine	Selenium, possibly vanadium	*Acute*: gastrointestinal disturbance (vomiting and diarrhoea), metabolic acidosis, seizure, stupor, delirium and collapse. *Sensitivity reactions*: iodide mumps, iododerma, iodide fever *Chronic*: disruption in thyroid function	0.15 mg	0.15 mg	GUL†: 0.5 mg
Manganese	Iron, fibre, phytate, calcium, phosphorus, magnesium, possibly alcohol	*Cumulative*: 'Manganism' – a Parkinson's disease-like neurotoxic condition; possible muscle pain, fatigue, tremor, memory problems and impaired reflexes.	Not specified	Not specified	GUL†: 4 mg
Molybdenum	Copper, sulphates	diarrhoea, anaemia, increased uric acid, occupational pneumoconiosis	Not specified	Not specified	No SUL* or GUL† can be determined
Nickel	Iron, possibly magnesium	*Acute*: gastrointestinal disturbances (due to sensitivity?), visual disturbance, headache, dizziness, wheezing, cough *Chronic* inhalation associated with lung cancer	Not specified	Not specified	No SUL* or GUL† can be determined.

Table I: Trace elements (continued)					
Substance	**Interaction**[1]	**Adverse Effects**[1]	**Proposed RDA**[3]	**'Old' RDA**[4]	**EVM**[1]
Selenium	Iodine, other metals, ascorbic acid, metabolism and toxicities of some 'xenobiotics'**¶	*Acute*: hypersalivation, emesis, garlic aroma on the breath, gastrointestinal effects, hair loss, neurological disturbance, tachycardia, fatigue *Chronic*: 'selenosis', changes to hair and nails, skin lesions, peripheral hypo-aesthesia, tingling in hands and feet (acro-parasthaesiae), pain, hyperreflexia; numbness, convulsions, paralysis Selenium sulphide is carcinogenic. Cumulative toxicity occurs	0.055 mg	Not specified	SUL*: 0.45 mg
Tin (not an essential trace element) ††	Zinc (possibly selenium)	*Acute*: gastrointestinal effects, headache, chills	Not specified	Not specified	GUL†: 13 mg‡‡
Vanadium (not a proven essential trace element)	Iron?	by inhalation – diverse toxic effects on respiratory, digestive, central nervous systems, kidney, skin; oral –abdominal cramps, loose stools, 'green tongue'; fatigue, lethargy	Not specified	Not specified	No SUL* or GUL† can be determined.
Zinc	Copper, iron, magnesium, calcium, fluoroquinolone antibiotics	*Acute*: abdominal pain, nausea, vomiting, lethargy, anaemia and dizziness *Chronic*: secondary deficiency of copper causing hypocupraemia, impaired iron mobilisation, anaemia, leukopaenia, neutropaenia, decreased superoxide dismutase (SOD) (particularly erythrocyte SOD), decreased caeruloplasmin, decreased cytochrome C oxidase, increased plasma cholesterol, increased LDL:HDL cholesterol, decreased glucose clearance, decreased methionine and leucine enkephalins, abnormal cardiac function, impairment amylase and lipase Possibly atherogenic in excess. HbA1c is increased in conditions of zinc excess	15 mg	15 mg	SUL*: 25 mg

*SUL: Safe Upper Level for daily supplementary intake in a 60kg adult over a lifetime
†GUL: the daily supplementary intake that would not be expected to be associated with adverse effects in a 60kg adult over a lifetime
‡excluding chromium picolinate which is not recommended by the FSA[2] until further safety data are available
§cobalt is an integral part of Vitamin B12 – 'cyano***cobal***amin'
¶no added inorganic germanium is recommended
**xenobiotics = medicinal drugs, agricultural chemicals, industrial chemicals, environmental contaminants and other exogenous substances[11]
††when present in food, usually a contaminant
‡‡U.K. regulatory limit of 200 mg/kg for the concentration of tin in foodstuffs

children.[6] (A cynic must surely wonder whether potentially toxic vanadium is considered preferable to methylphenidate [Ritalin®] by the parents [and teachers] of children afflicted with this problem.)

FREE RADICALS AND ANTIOXIDANTS

One of the reasons the widespread use of 'dietary' and 'nutritional' supplements has flourished, is because of fear-based, partially true, information about free radicals and their dangers. The widely recommended 'antidote' is to ingest antioxidants – usually in the form of quite expensive dietary supplements (because our 'modern day diet' supposedly does not provide all our nutritional needs).

Note that a free radical could be any molecule with an unpaired electron, thus making it unstable. Free radicals are constantly being formed (and neutralised!) through the normal processes of metabolism and excretion. It is when the production of free radicals becomes excessive that the potential for cellular (oxidative) damage is enhanced. This is also referred to as 'oxidative stress' or 'oxidative injury'. The half life of a free radical can be of the order of 10^{-9} seconds.[7] References in the lay press to 'the accumulation of free radicals', and/or 'increasing levels' of free

Table II: Minerals

Substance	Interaction[1]	Adverse Effects[1]	Proposed RDA[2]	'Old' RDA[3]	EVM[1]
Calcium	Phytic acid, iron, zinc, aluminium:phosphorus complexes (antacids)	progressive lethargy, confusion, coma, headache, elevated cerebrospinal fluid protein, convulsions, milk alkali syndrome, abdominal pain, hypertension, tissue calcification, impaired renal function, irreversible renal calcification when excess calcium, hyperphosphataemia and metabolic alkalosis	1100 mg	800 mg	GUL*: 1500 mg
Iron	copper, manganese, zinc, chromium, calcium	*Systemic*: Liver damage, metabolic acidosis, coagulopathies and cardiovascular collapse *Local*: gastric or oesophageal ulceration, gastrointestinal effects, especially constipation *Chronic*: haemochromatosis, Iron may act as a catalyst in the initiation of free radical-mediated reactions	14 mg	14 mg	GUL*: 17 mg
Magnesium	Calcium, possibly nickel Urinary excretion affected by calcitonin, thyroxine, glucocorticoids, glucagons and angiotensin	Reversible osmotic diarrhoea	350 mg	300 mg	GUL*: 400 mg
Phosphorus	Aluminium-containing antacids, calcium	Osmotic diarrheoa, nausea, vomiting	880 mg	800 mg	GUL*: 250 mg
Potassium	Sodium, magnesium, thallium	*Acute*: heart failure, cyanosis, cardiac arrest *Chronic*: abdominal pain, nausea, vomiting, diarrhoea, ulceration: oesophagus, stomach, duodenum, ileum	Not specified	Not specified	GUL*: 3700 mg (for supplements)‡
Silicon	copper, zinc, germanium	Silicosis	Not specified	Not specified	SUL†: 700 mg

*GUL: the daily supplementary intake that would not be expected to be associated with adverse effects in a 60kg adult over a lifetime
†SUL: Safe Upper Level for daily supplementary intake in a 60kg adult over a lifetime
‡Infants, older subjects and patients with conditions such as pre-existing hyperkalaemia, renal disease, acidosis, insulin deficiency or digitalis intoxication should not take potassium supplementation without medical advice.

radicals are blatantly incorrect and misleading. It is rather the unchecked series of chain reactions initiated by free radicals and reactive oxygen and nitrogen species (see below) that may contribute to the development of various disease states.

These infinitesimal half-lives are not directly measurable *in vivo* and, as with so many other areas of medicine, surrogate markers have become available or are being sought to measure oxidative stress/oxidative damage. Potential biomarkers include:

- lipid peroxidation products (e.g. lipid hydroperoxides; malondialdehyde and other aldehydic decomposition products; exhaled pentane and ethane; F_2-isoprostanes);
- DNA oxidation products (8-oxo-deoxyguanosine, 8-oxydeoxy-adenosine, thymol glycol);
- protein carbonyls;
- nitrated protein derivatives.[8]

The collective labels for the known substances most often produced by the body or from external sources are 'reactive oxygen species' (ROS) and 'reactive nitrogen species' (RNS).[8] These could also be thought of as 'pro-oxidants'.

REACTIVE OXYGEN AND NITROGEN SPECIES[8]

ROS includes several oxygen *radicals* and *nonradicals*.

Oxygen radicals (the unpaired electron is represented by a *)

- superoxide (O_2^{*-})
- hydroperoxyl (HO_2^*) [pronated form of superoxide]
- hydroxyl (OH*)
- peroxyl (RO_2^*) [R = any molecule]
- alkoxyl (RO*) [R = any molecule]

Oxygen nonradicals (oxidising agents easily converted into oxygen radicals)

- hydrogen peroxide (H_2O_2)
- hypochlorous acid (HOCl)
- ozone (O_3)
- singlet oxygen ($^1O_2$)

RNS likewise includes *radicals* and *nonradicals*.

Nitrogen radicals (the unpaired electron is represented by a *)

- nitric oxide (NO*)

Nitrogen nonradicals (easily converted into nitrogen radicals)

- peroxynitrite ($ONOO^-$)
- peroxynitrous acid (ONOOH)

An under-emphasised aspect of the production of reactive species is their beneficial function in terms of killing microbes (e.g. ROS produced by activated phagocytes[8]) and their interference in cancer cell propagation. It must be noted also that the mechanism of action of certain drugs involves the production of reactive species, and it is possible that excess use of 'supplements' may well interfere with the efficacy of these drugs (e.g. Vitamin E inhibits cisplatin-induced apoptosis in MCF-7 breast cancer cells.[9])

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Dietary Antioxidants and Related Compounds, of the Food and Nutrition Board of the Institute of Medicine developed the following definition of a dietary antioxidant:

A dietary antioxidant is a substance in foods that significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiological function in humans.[8]

The development of this definition was based on the following criteria: 1) the substance is found in human diets; 2) the content of the substance has been measured in foods commonly consumed; and 3) in humans, the substance decreases the adverse effects of reactive oxygen and nitrogen species *in vivo*.[8]

The mechanisms of action of antioxidants are postulated to include:

1. Decreasing ROS or RNS formation.
2. Binding metal ions needed for catalysis of ROS generation.
3. Scavenging ROS, RNS or their precursors.
4. Up-regulating ***endogenous*** antioxidant enzyme defences.
5. Repairing oxidative damage to biomolecules.
6. Influencing and upregulating repair enzymes.[8] (my emphasis)

It is important to note (contrary to most advertisements for supplements) that:

'The effectiveness of each dietary antioxidant depends on ***which*** ROS or RNS is being scavenged, ***how*** and ***where*** they are generated, the ***accessibility*** of the antioxidants to this site and ***what*** target of damage, or oxidisable substrate, is involved.'[8] Based on this, it would appear that simply taking an antioxidant supplement is rather like gambling. The chances of the antioxidant molecules being present in the right place at the right time cannot be predicted.

However, one of the indirect (derived) measures of the effectiveness of an antioxidant is known as 'the oxygen radical-absorbing capacity (ORAC). The ORAC assay is a measure of the total antioxidant capacity of the serum derived from the sum of all serum antioxidants whether produced by the body (endogenous, such as glutathione and urate) or taken from the diet (exogenous, such as vitamins C and E and flavonoids).'[10] Even this measure does not indicate what is happening at a tissue level.

CONCLUSION

Usually doctors are accused of 'medicalising' normal functions (e.g. childbirth) or normal emotions (e.g. grief) – but the promotion of a lifestyle of supplement-taking is indicative of a (gullible?) general public which has been convinced that everyone needs to medicalise their food intake.❐

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