

EXPERT GROUP ON VITAMINS AND MINERALS

REVIEW OF PANTOTHENIC ACID

The attached review is a slightly amended version of the paper first presented to the Expert Group on the meeting on 9 February 2001 and again in October 2001 and April 2002.

The following annexes are included with this paper:

- Annex 1 Tables and figures referred to in the review
- Annex 2 Intakes of pantothenic acid from food and supplements in the UK
- Annex 3 Summary table of selected nutrition related information and existing guidance on intakes

Expert Group on Vitamins and Minerals Secretariat
August 2002

PANTOTHENIC ACID

1. The term pantothenic acid derives from the Greek work *pantothern*, meaning “from all quarters”, and refers to the presence of this compound in virtually all biological materials.

Chemistry and geochemistry

2. Pantothenic acid [β -alanine, N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-, (R)- (9CI); vitamin B₅; CAS Registry Number 79-83-4; C₉-H₁₇-N-O₅; RMM, 219] is synthesised by micro-organisms via an amide linkage of pantoic acid and β -alanine subunits. Pantetheine, which is an essential growth factor for *Lactobacillus bulgaricus*, consists of pantothenic acid linked to a β -mercaptothylamine group. Biologically, the compound is a component of coenzyme A (CoA), which is composed of 4'-phosphopantetheine linked by an anhydride bond to adenosine 5'-monophosphate, modified by a 3'-hydroxyl phosphate (Figure 1.). 4'-Phosphopantetheine is also found covalently linked to various proteins, particularly those involved in fatty acid metabolism (Plesofsky-Vig, 1999).

3. Pure pantothenic acid is present in the form of a yellow viscous oil, which is chemically synthesised by condensation of D-pantolactone with β -alanine. The compound is freely soluble in water, stable in neutral solution, but unstable to acids, bases and heat. Supplements are generally available as the synthetic (D-enantiomer) calcium salt [pantothenate] (white crystals), or the alcohol, panthenol [pantohenol, pantothenyl alcohol] (a colourless liquid), which are more stable than pure pantothenic acid. Calcium pantothenate and panthenol are highly soluble in water and are rapidly converted to the free acid within the body (*data cited by* HSDB, accessed at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>, August 2001; Roche Vitamins, accessed at <http://www.roche-vitamins.com/home/what/what-hnh/what-hnh-vitamins/what-hnh-panto.htm> July 2002; Plesofsky-Vig, 1999).

Natural occurrence

4. Pantothenic acid is present in virtually all plant, animal and microbial cells.

Occurrence in foods, food supplements and medicines

Foods

5. Data regarding the absolute levels of pantothenic acid in foods are limited by methods of analysis (in particular, in the liberation of the pantothenic acid moiety from bound forms such as CoA or fatty acid synthetase) (discussed by Tahiliani & Beinlich, 1991). Chicken, beef, potatoes, oat cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, cauliflower, molasses and whole grains are reported to be major sources of this vitamin, whilst very high levels are present in royal bee jelly and in the ovaries of tuna and cod (Walsh *et al.*, 1981; Plesofsky-Vig, 1999). Cows' milk contains approximately 3.5 mg/l pantothenic acid; human milk contains approximately 2 mg/l (cited by HSDB, accessed at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>, August 2001). Pantothenic acid in foods is relatively stable at neutral pH, but cooking is reported to destroy 15-50 % of the vitamin in meats

(Robinson, 1966), whilst processing of vegetables leads to pantothenate losses of 37-78% (Tahiliani & Beinlich, 1991). Refined grains, fruit products, and meats or fish with added fats or cereal extenders are reported to be lower in pantothenic acid content than their fresh equivalents (Schroeder, 1971; Food and Nutrition Board, 2000).

Food fortification, supplements and medicines

6. Pantothenic acid derivatives sold as supplements or medicines are prepared synthetically, as calcium pantothenate or panthenol, which are more stable than pure pantothenic acid. Calcium pantothenate is generally included in multivitamin preparations, whilst panthenol is the more common form used in monopreparations, which are available in a wide variety of pharmaceutical forms (for example solutions for injection and local application, aerosols, tablets, ointments, creams) (cited by Roche Vitamins, accessed at:

<http://www.roche-vitamins.com/home/what/what-hnh/what-hnh-vitamins/what-hnh-panto.htm>, July 2002).

For the treatment of deficiency due to impaired absorption, intravenous (*i.v.*) or intramuscular (*i.m.*) injections (500 mg several times per week) are recommended. Doses up to 1000 mg per 6 hours may be used for postoperative ileus (paralysis of the intestine) (cited by Roche Vitamins, accessed at: <http://www.roche-vitamins.com/home/what/what-hnh/what-hnh-vitamins/what-hnh-panto.htm>, July 2002).

Multivitamin preparations generally contain \approx 15-100 mg calcium pantothenate per tablet (cited by HSDB, accessed at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>, August 2001). The OTC directory (OTC, 2001) indicated that UK dietary supplements generally contain 6-10 mg pantothenic acid.

7. Some breakfast cereal manufacturers fortify their products, on a voluntary basis, with pantothenic acid usually to a level of 5-6 mg/100 g.

Licensed medicinal products for oral use

8. Nine products containing pantothenic acid may be sold in supermarkets and other retail outlets, without the supervision of a pharmacist, for the prevention of deficiency, in convalescence, for the elderly and for those on restricted diets. All contain a range of other nutrients. The highest daily dose authorised is 50 mg. Fourteen products can only be sold in pharmacies. They are used where intake and absorption are reduced, for supplementation of special diets and in food intolerance. All contain a range of other nutrients. The authorised doses are no greater than those for products on general sale.

Intake/Exposure

9. Pantothenic acid requirements are provided by the diet. In ruminants the compound may be obtained *via* synthesis by intestinal microflora (Peterson & Peterson 1945, cited by Fox 1984). Synthesis by intestinal microflora has also been noted in mice (Stein & Diamonds, 1989), but the potential contribution of this source to body pantothenic acid levels in humans has not been reported (Food and Nutrition Board, 2000).

Food

10. Annex 1 gives details of intakes of pantothenic acid from food and supplements. Data from the 1990 Dietary and Nutritional Survey of British Adults showed mean pantothenic acid intakes of 5.1 and 6.6 mg/day (all sources), or 4.5 and 6.3 mg/day (food sources only), for women and men, respectively (Gregory *et al.*, 1990).

Recommended amounts

11. Dietary Reference Values for pantothenic acid within the UK have not been established. The Committee on Medical Aspects of Food and Nutrition Policy have set a Safe Intake¹ of 3-7 mg/day for adults and 1.7 mg/day for infants (DH, 1991).

12. Adequate Intake (AI) values for pantothenic acid in the USA, based on estimation of the intake required to replace urinary excretion, are 0.2 mg/kg bw/day (infants up to 12 months), 2 mg/day (children aged 1-3 years), 3 mg/day (children aged 4-8 years), 4 mg/day (children aged 9-13 years), 5 mg/day (adults and adolescents \geq 14 years), 6 mg/day (pregnancy) and 7 mg/day (lactation) (Food and Nutrition Board, 2000). RDA values for pantothenic acid have not been established.

Analysis of tissue levels

13. Blood, urine or tissue pantothenic acid levels may be measured by microbiological or animal (chick) conditional growth assays (based upon the requirement for this vitamin as an essential growth factor) or by radioimmunoassay (Plesofsky-Vig 1999 and references therein). Assays of pantothenic acid in biological materials other than urine require that the compound is first hydrolysed from CoA.

14. Normal values for pantothenic acid in whole blood have been reported as within the range of \approx 1.5-9 μ mol/l (\approx 0.3-2 mg/l) (Food and Nutrition Board 2000 *and refs therein*), although there is wide inter- and intra-individual variation. Eissenstat *et al* (1986) reported an average erythrocyte pantothenic acid concentration of 0.3 mg/l (1.5 μ mol/l) in a study of 63 healthy adolescents. Plasma concentrations are much lower than, and do not correlate with, those in whole blood due to the absence of CoA and other co-enzymes containing this vitamin. Urinary excretion (reported as \approx 2.6 mg/day (\approx 11.7 μ mol/day) on a typical American diet (Tarr *et al.*, 1981)), is strongly correlated with intake (Hodges *et al.*, 1958, Fry *et al.*, 1976, Eissenstat *et al.*, 1986).

15. Johnston *et al* (1981) reported an average pantothenic acid content of 6.7 mg/l (\approx 30 μ mol/l) in human breast milk.

Bioavailability

16. Very limited data are available regarding the bioavailability of dietary pantothenic acid. In a recent review of this subject, van den Berg (1997) stated that no dietary factors are known that affect pantothenate availability. One study (Tarr *et al.*,

¹ A level or range of intake at which there is no risk of deficiency, and below a level where there is a risk of undesirable effects.

1981) found that pantothenic acid in natural foods was $\approx 50\%$ bioavailable compared with the pure vitamin (calcium pantothenate) given in a formula diet, as assessed by subsequent urinary excretion of the vitamin.

Interactions

Other B vitamins

17. Koyanagi *et al.* (1969) reported that supplementation of adult volunteers with 5 mg* thiamin or, to a lesser extent, 5 mg* riboflavin increased mean serum and urinary pantothenic acid levels in groups of 5 adult volunteers, although the data upon which these conclusions were based are limited.

[* presumably per day, although not clearly stated]

18. Yacowitz *et al.* (1951) reported a sparing action of vitamin B₁₂ on pantothenic acid in chicks. Liver (free) pantothenic acid levels decreased when vitamin B₁₂-deficient chicks were subsequently supplemented with vitamin B₁₂, which has been suggested as an effect of vitamin B₁₂ in aiding the conversion of pantothenic acid to CoA. Treatment of vitamin B₁₂-deficient rats with pantothenic acid reduced liver vitamin B₁₂ levels, whilst pantothenic acid-deficient rats fed large doses of vitamin B₁₂ showed increased survival rates (Okuda *et al.*, 1962).

19. There is evidence to suggest that biotin and pantothenic acid may share a common carrier-mediated active uptake mechanism in the gastrointestinal tract (Said *et al.*, 1998, Chatterjee *et al.*, 1999) and other tissues, for example the heart (Beinlich *et al.*, 1990), placenta (Grassl 1992, Prasad *et al.*, 1997, Wang *et al.*, 1999) and blood-brain barrier (Spector & Mock, 1987). However, the physiological and nutritional implications of interactions between these two vitamins are currently unknown.

Ascorbic acid

20. Guinea pigs fed ω -methylpantothenic acid (an antagonist of pantothenic acid) showed decreased serum ascorbic acid levels, suggesting that pantothenic acid may be necessary for efficient ascorbic acid utilisation (Pudelkewicz & Roderuck, 1960). In pantothenic acid-deficient rats, supplementation with either pantothenic acid or ascorbic acid lessened the effects of pantothenic acid deficiency and improved reproductive performance and birth weight, compared to pantothenic acid-deficient animals fed control diets (Everson *et al.*, 1954; Barboriak & Krehl, 1957).

Copper

21. Latymer & Coates (1981) reported that supplementation with copper sulphate (250 mg/kg diet) was associated with reduced pantothenic acid levels and/or pantothenic acid deficiency in chicks.

Dietary fat

22. Sewell *et al.* (1962) (published abstract) reported that pigs fed a pantothenic acid-deficient, high-fat diet developed deficiency signs, failed to gain weight and

showed a lower feed efficiency ratio more quickly than pigs fed a pantothenic acid-deficient, low-fat diet.

Dietary protein

23. Pantothenic acid-deficient rats fed a high protein diet showed accelerated growth and survival compared with those fed a low-protein diet (Nelson & Evans, 1945; Tao & Fox, 1976). Pantothenic acid has been shown to improve growth rate in pigs fed low, but not high, protein diets (Luecke *et al.*, 1952).

Oral contraceptives

24. Lewis & King (1980) reported that high-dose oral contraceptive use did not affect blood or urinary pantothenic acid levels in a 12-day study of 13 young women.

L-pantothenate

25. Studies in mice have suggested that L-pantothenate is a metabolic antagonist of the biologically active D-enantiomer. Male ICR mice fed a pantothenic acid-deficient basal diet supplemented with L(-)-calcium pantothenate showed a greater reduction in growth rate than animals given the pantothenic acid-deficient basal diet only (both groups as compared with mice fed a pantothenic acid-deficient diet supplemented with D(-)-calcium pantothenate) (Kimura *et al.*, 1980).

Absorption

26. Approximately 85% of dietary pantothenic acid is present as CoA or phosphopantetheine (cited in Bender & Bender, 1997). Studies using isolated rat intestine indicated that orally administered CoA was hydrolysed to pantothenic acid within the intestinal lumen *via* the formation of dephospho-CoA, phosphopantetheine and pantetheine. Pantetheine and pantothenic acid, but not CoA, dephospho-CoA, or phosphopantetheine, were readily absorbed by intestinal tissues (Shibata *et al.*, 1983). Pantetheinase, an enzyme which can hydrolyse pantetheine and pantethine, has been identified in rat intestinal luminal cells (Ono *et al.*, 1974; Shibata *et al.*, 1983; Wittwer *et al.*, 1985). Although pantothenic acid may be absorbed by passive diffusion (the predominant process at high intraluminal pantothenate concentrations), a saturable, sodium-dependent, active transport mechanism has also been described (Fenstermacher & Rose 1986, Stein & Diamonds 1989). Studies in mice indicated that the kinetics of this active intestinal transport process for pantothenate were not affected by different dietary intake levels of the vitamin (Stein & Diamonds, 1989).

27. Studies in Caco-2 cells have shown that a sodium-dependent carrier-mediated transport mechanism, shared by both biotin and pantothenic acid, is present at the apical membrane of these cells. Thus absorption of pantothenic acid synthesised by the microflora of the large intestine is postulated (Said, 1999).

Distribution and metabolism

28. Absorbed pantothenic acid is transported to body tissues *via* the blood, primarily as bound forms in erythrocytes (Eissenstat *et al.*, 1986). Plasma levels do

not correlate well with dietary intake (Srinivasan *et al.*, 1981, Song *et al.*, 1985). Baker *et al.* (1969) reported a large increase in erythrocyte pantothenate levels after i.v. injection of 7 adult male volunteers with a multivitamin mixture including 45 mg D-pantethol. Maximum plasma pantothenate levels occurred at 3 minutes post-injection and subsequently decreased, suggesting that the compound is taken up rapidly by erythrocytes or other tissues (Tahiliani & Beinlich, 1991).

29. Tissue-distribution studies in rats showed that, 5 hours after intraluminal administration of ^{14}C - pantothenate or ^{14}C - CoA, approximately 40% of the ^{14}C was present in muscle, 10% in the liver and 10% in the intestine, whilst plasma levels were minimal (Shibata *et al.*, 1983). In dogs, oral dosing with ^{14}C - pantothenic acid showed a maximum plasma response at 2-2.5 hours, followed by declining concentrations, whereas plasma ^{14}C levels fell rapidly during the first 2 hours after i.v. injection, with a subsequent half life of 2.5 hours (Taylor *et al.*, 1974, cited by Tahiliani & Beinlich, 1991). The maximum total blood pantothenic acid concentration was observed 2-4.5 hours after oral ingestion of pantetheine or calcium pantothenate in rats (Ono *et al.*, 1974, cited by Tahiliani & Beinlich, 1991).

30. Analysis of the pantothenic acid content of rat tissues showed high concentrations in the heart and kidneys (284 and 245 nmol/g dry weight, respectively) (Reibel *et al.*, 1981, cited by Tahiliani & Beinlich, 1991).

31. Pantothenic acid is an essential component for the synthesis of CoA and, thus, the majority of tissues transport the compound into cells, *via* an active sodium cotransport mechanism (Barbarat and Poderin, 1986; Lopaschuk *et al.*, 1987; Grassl, 1992; Prasad *et al.*, 1999; Wang *et al.*, 1999).

32. Within the cell, pantothenate kinase catalyses the phosphorylation of pantothenic acid – shown in bacteria and rat hearts to be the primary regulatory point of CoA synthesis – which is inhibited by the end products, CoA and acyl CoA (Robishaw *et al.*, 1982). Subsequently, 4'-phosphopantothenic acid undergoes an ATP-dependent condensation reaction with cysteine to produce 4'-phosphopantethenoylcysteine, which is carboxylated to 4'-phosphopantetheine. CoA is formed by the sequential transfer of adenosine monophosphate and phosphate from ATP to 4'-phosphopantetheine (Brown 1959, cited by Plesofsky-Vig 1999) (Figure 2). The ultimate site of CoA synthesis is assumed to be the mitochondrion as the majority of CoA (which does not cross the mitochondrial membrane) is found within these organelles (Robishaw *et al.*, 1982, cited by Plesofsky-Vig 1999). In addition to linkage to diphospho-adenosine in CoA, 4'-phosphopantetheine can also be covalently linked to amino acid residues in a number of cellular proteins.

Excretion

33. Pantetheine, formed by the stepwise breakdown of CoA, is hydrolysed to cysteamine and pantothenate, which is excreted in the urine (Wittwer *et al.*, 1983). Urinary excretion levels are reported to be highly correlated with dietary intake (Food and Nutrition Board, 2000 and refs therein). Adults consuming a diet containing 5-7 mg/day pantothenic acid excrete 2-7 mg/day (9-32 $\mu\text{mol/day}$) in the urine and 1-2 mg/day (4.5-9 $\mu\text{mol/day}$) in the faeces (cited in Bender & Bender, 1997). Urinary

excretion levels in subjects given experimental diets providing 10 mg/day pantothenic acid were 4-7 mg/day (18-32 $\mu\text{mol/day}$) (Fry *et al.*, 1976).

34. It has been reported that urinary pantothenic acid excretion is increased in human diabetics, although the converse was observed in alloxan-diabetic rats (Hatano *et al.*, 1967; Reibel *et al.*, 1981).

Function

35. Pantothenate, usually in the form of CoA-containing species (e.g. acetyl CoA, succinyl CoA) performs multiple roles within cellular metabolism and in the synthesis of many essential molecules. These various roles are summarised below (reviewed by Plesofsky-Vig, 1999):

- 1] Within the tricarboxylic acid cycle, β -oxidation of fatty acids and oxidative degradation of amino acids.
- 2] Fatty acid and membrane phospholipid synthesis.
- 3] Amino acid synthesis (leucine, arginine, methionine).
- 4] Synthesis of isoprenoid derivatives, such as cholesterol, steroid hormones, dolichol, vitamin A, vitamin D, haem A.
- 5] Synthesis of δ -amino-laevulinic acid, the precursor of porphyrin and corrin rings (vitamin B₁₂, haemoglobin, cytochromes).
- 6] Synthesis of neurotransmitters (eg, acetylcholine).
- 7] Acetylation, acylation, myristylation, palmitoylation and isoprenylation of proteins.

36. Added at optimal concentrations of 3 $\mu\text{mol/l}$ to medium containing hamster 1-cell embryos, pantothenic acid has been shown to significantly stimulate blastocyst development (McKiernan and Bavister, 2000). Following embryo transfer, the percentage of live foetuses recovered was significantly higher than for embryos cultured in media alone. It is suggested that this effect is due to pantothenic acid enabling or increasing the formation of acetyl-CoA and thus stimulating oxidative metabolism.

Deficiency

37. Deficiency of pantothenic acid in humans is extremely rare. Such deficiency has been implicated as a cause of "burning feet" syndrome (nutritional melalgia) reported in severely malnourished subjects (for example, allied prisoners in Asia during World War II (Glusman, 1947), for which one report described rapid relief upon treatment with pantothenic acid (Gopalan, 1946, cited by Glusman, 1947). Experimentally, pantothenic acid deficiency has been induced in human subjects by feeding diets virtually devoid of the vitamin (Fry *et al.*, 1976), or by the administration of a metabolic antagonist (ω -methyl pantothenic acid) (Hodges *et al.*, 1958, 1959). Signs and symptoms exhibited by subjects given ω -methyl pantothenic acid included irritability and restlessness, fatigue, apathy, malaise, sleep disturbances, gastrointestinal complaints such as nausea, vomiting and abdominal cramps, neurobiological symptoms such as numbness, parasthesias, muscle cramps and staggering gait, hypoglycaemia and an increased sensitivity to insulin. Administration of hopantenate medication (a pantothenic acid analogue in which GABA replaces β -

alanine, and which at the time was not known to be a pantothenic acid antagonist) to mentally-retarded patients induced severe side effects including lactic acidosis, hypoglycaemia and hyperammonaemia, leading to acute encephalopathy (Otsuka *et al.*, 1990).

38. Experimental pantothenic acid deficiency in animals produced hypertrophy of the adrenal cortex, followed by haemorrhage and necrosis in rats, depressed haem synthesis and anaemia in monkeys, dermatitis, poor feathering and axon and myelin degeneration within the spinal cord of chickens (Robinson *et al.*, 1966 cited by Plesofsky-Vig, 1999). Deficiency-associated dermatitis and greying of the fur can be reversed by pantothenic acid treatment of rats, (although such deficiency is not associated with loss of hair colour in humans and treatment with the vitamin does not restore hair colour in humans) (Robinson 1966 and references therein).

39. A review (Bender, 1999) suggested that it was unlikely that fatty acid oxidation would be significantly affected by pantothenate deficiency. In an experimental study pantothenate deficient, alloxan-diabetic rats displayed little or no fall in tissue CoA compared to controls.

Overview of reported, non-nutritional, beneficial effects

40. Studies using animal models have shown non-nutritional beneficial effects of pantothenic acid. Addition of pantothenic acid increased energy metabolism in isolated skeletal muscle tissue in a mouse model of Duchenne muscular dystrophy (Even *et al.*, 1994). Nagiel-Ostaszewski and Lau-Cam (1990) reported that daily intraperitoneal injection with pantothenic acid protected rats against peroxidation and liver damage produced by carbon tetrachloride, whilst Slyshenkov *et al.* (1998) reported that prior treatment of rats with intragastric doses of panthenol protected the animals against some of the deleterious effects of gamma irradiation (see paragraph 78). It has also been reported that there are indications that the compound may improve surgical wound healing (Aprahamian *et al.*, 1985; Lacroix *et al.*, 1988) and *in vitro* studies have shown that pantothenate reduces polymorphonuclear neutrophil (PMN) response to stimulatory peptides and cytokines (Kapp & Zeck-Kapp, 1991). Treatment with pantothenic acid increased levels of CoA in HepG2 cells, with increased hippurate formation in sodium benzoate-treated cells, and it has been suggested that the compound may have a beneficial effect on sodium benzoate therapy in children with hyperammonaemia and nonketotic hyperglycinaemia (Palekar, 2000).

41. Low blood pantothenic acid levels have been reported in patients with rheumatoid arthritis (Barton-Wright & Elliot, 1963), and some authors claim that supplementation with pharmacological doses of the vitamin may alleviate the symptoms of this condition. Such claims have not been widely tested in controlled human studies. There are numerous case reports in which pharmacological doses of pantothenic acid compounds have been used to treat the symptoms of lupus erythematosus (see the "Human Supplementation Studies section of this report), although again the therapeutic value of such treatment has not been widely assessed in controlled studies.

Toxicity

Human toxicity

42. Pantothenic acid is generally considered as safe, even at extremely high doses, as excesses of the compound are mostly excreted in the urine, rather than being stored in the tissues. Very high oral doses (generally > 1 g/day) of pantothenic acid compounds have been associated with diarrhoea and gastrointestinal disturbances.

Acute toxicity

43. There are no reports of acute toxic effects in humans of pantothenic acid, or its commonly available pharmaceutical forms, other than gastrointestinal disturbance (see the “Human Supplementation Studies” section of this report).

Neurotoxicity

44. Data have not been identified regarding the potential neurotoxicity of pantothenic acid, or its commonly available pharmaceutical forms, in humans.

Carcinogenicity

45. No data were identified regarding the potential carcinogenic effects of pantothenic acid, or its commonly-used pharmaceutical forms, in humans.

Genotoxicity

46. Genotoxicity studies in humans of pantothenic acid, or its commonly-used pharmaceutical forms, have not been identified.

Reproductive toxicity

47. Very few data are available regarding the effects of high-dose pantothenic acid supplementation during pregnancy.

48. One case report described supplementation of an epileptic woman (receiving valproate and ethosuximide treatment) with high-dose multivitamins and minerals (including 70 mg/day “pantothenate”) during weeks 13-28 of gestation (Baggot *et al.*, 1999). Foetal head growth was normal up to 30.4 weeks, but slowed between 30.4 and 37.1 weeks of gestation, after the vitamin therapy had been discontinued.

Human supplementation studies (Table 1)

49. Welsh (1952, 1954) reported an open study in which patients were treated with extremely high doses of pantothenic acid derivatives, with the aim to alleviate symptoms of lupus erythematosus. A total of 67 patients was treated, for periods of up to 3 years, with daily doses* of calcium pantothenate ($\leq 10-15$ g), pantothenyl alcohol (panthenol) ($\leq 10-15$ g) or sodium pantothenate ($\leq 5-10$ g), in combination with 1-2 mg vitamin E. Some patients showed improvement of symptoms which the authors considered to be related to the supplementation, although it was also noted that 11

patients developed new lesions whilst undergoing therapy. Symptoms of transient nausea and gastric distress were reported as the only side effects of the therapy. The authors also stated that “varying combinations and massive dosages of pantothenic acid derivatives and vitamin E preparations were given to 154 patients who had diseases other than lupus erythematosus. There was no complication, except for gastric distress...”

[* large doses of at least up to 15 g/day were given, although it is not clear whether the different forms of pantothenic acid were given in combination or singly]

50. Ralli (1952) carried out an open study to assess the effects of prior supplementation with very high daily doses of calcium pantothenate on the response to cold water stress in adult men. Twelve men were initially assessed by immersion in water at 9°C for 8 minutes, followed by blood and urine analyses. The subjects were then given calcium pantothenate supplementation (10 g/day, for 6 weeks) following which the stress response tests were repeated. The author reported that supplementation was associated with reduced eosinophilic response to stress, increased blood and urinary ascorbic acid levels, and a decreased uric acid/creatinine ratio, effects which persisted for up to 4 months after the therapy was discontinued. No side effects of the therapy were reported.

51. Goldman (1950) described the use of panthenol for the treatment of lupus erythematosus. Patients with acute disseminated ($n = 9$), subacute disseminated ($n = 10$) or discoid ($n = 27$, although the individual levels and durations of supplementation were not reported for patients in this group) lupus erythematosus were given oral panthenol supplementation, at various dosage levels up to 8-10 g/day, for various periods ranging from 5 days to \approx 6 months. In some cases, patients were also receiving other therapies (eg, penicillin, ACTH). The authors stated that “There is apparently no toxicity of panthenol even at dosage levels of 8-10 grams daily, (the) maximum daily dose. Patients have been maintained on 1 and 2 grams daily for as long as six months.” Improvement in symptoms of lupus erythematosus was observed in some cases. Three patients with the acute form of the disease died, but the authors did not relate this to the panthenol therapy.

52. A randomised, double-blind, placebo-controlled study was carried out to assess the effects of high-dose pantothenate supplementation in alleviating symptoms of arthritis. A total of 94 patients, diagnosed with osteoarthritis ($n = 59$), rheumatoid arthritis ($n = 27$), gout ($n = 2$), spondylitis ($n = 4$), psoriatic arthritis ($n = 1$) or unspecified diagnosis ($n = 1$) were treated with either calcium pantothenate (total daily dose – 0.5 g on days 1-2, 1.0 g on days 3-5, 1.5 g on days 6-9, 2.0 g from day 10 onwards) or placebo for a period of 8 weeks. Supplementation was associated with a significant reduction of some patient-reported arthritis symptoms in the rheumatoid arthritis sub-group, but not with significant effects in the study group as a whole. Regarding adverse effects of the therapy, the authors stated that “... no side effects were recorded in 43 patients (91%) on calcium pantothenate as compared to 37 (79%) on placebo.” (General Practitioner Research Group, 1980).

53. A published abstract by Litoff *et al.* (1985) described a randomised, placebo-controlled, double-blind, crossover study of the effects of pantothenic acid supplementation (2 g/day, 14 days) on exercise performance in 7 trained, male

distance runners. Supplementation was associated with reduced venous blood lactate concentration and reduced oxygen consumption, as compared with placebo treatment. No side effects of the therapy were reported.

54. Webster (1998) carried out a randomised, double-blind, placebo-controlled, crossover study to assess the effects of pantothenic acid/pantethine therapy on exercise performance in 6 highly-trained cyclists. For each subject, 2 testing (cycling performance) sessions were carried out, separated by a 21-day washout period. One testing session was carried out immediately after 7-day supplementation with a combination of 1.8 g/day of a 55% pantethine; 45% pantothenic acid mixture + 1 g/day allithiamin, whilst the alternative session was carried out after 7-day supplementation with placebo. No significant differences were identified between assessed parameters of cycling performance associated with active or placebo treatment. No side effects of the therapy were reported.

55. A 2-stage trial was carried out to investigate the effectiveness of megavitamin therapy in improving the behaviour of 41 children with attention deficit disorders (Haslam *et al.*, 1984). Stage 1 was carried out as a 3-month open design, in which all children were given combined vitamin supplements, as follows;

- Weeks 1-2: Zero supplementation.
- Weeks 3-4: 0.4 g calcium pantothenate, 0.2 g pyridoxine, 1.0 g ascorbic acid, 1.0 g niacinamide.
- Weeks 5-6: 0.6 g calcium pantothenate, 0.3 g pyridoxine, 1.5 g ascorbic acid, 1.5 g niacinamide.
- Weeks 7-8: 0.8 g calcium pantothenate, 0.4 g pyridoxine, 2.0 g ascorbic acid, 2.0 g niacinamide.
- Weeks 9-10: 1.0 g calcium pantothenate, 0.5 g pyridoxine, 2.5 g ascorbic acid, 2.5 g niacinamide.
- Weeks 11-14: 1.2 g calcium pantothenate, 0.6 g pyridoxine, 3.0 g ascorbic acid, 3.0 g niacinamide.

56. After a 6-week washout period, 7 of the 12 children who showed a positive response in stage 1 proceeded to stage 2. This second stage consisted of 4x 6-week trial periods carried out as a double-blind, placebo-controlled, repeated crossover design (randomly assigned in the order PDPD, or DPDP, where P = placebo; D = drug). Supplementation levels were as for weeks 7-8 (4 subjects), 9-10 (1 subject) or 11-14 (2 subjects) of stage 1. There were no significant differences in behavioural outcomes between drug and placebo treatments.

57. Three children did not complete stage 1 of the study because of excessive vomiting, abdominal discomfort, or inability to swallow the vitamin capsules, whilst 5 of the 12 children who were invited to participate in stage 2 declined due to complaints including nausea, anorexia, gagging, and abdominal pain whilst taking the vitamins. Renal and liver function tests were performed on all children at baseline and upon completion of stage 1 of the trial, at which point "average" serum transaminase concentrations had risen from 27.14 ± 7.71 to 48.81 ± 29.08 ($P < 0.001$) and levels in 17 (42%) participants were considered to exceed the upper limit of the normal range of serum aspartate transaminase concentrations. Values returned to base-line 4-6 weeks after discontinuation of the therapy. The authors considered that it was

probable that niacinamide was responsible for these liver enzyme abnormalities although, as this vitamin was not tested separately, this hypothesis could not be confirmed (Haslam *et al.*, 1984).

58. Supplementation with 1.1 g/day (0.6 g/day orally, 0.5 g/day *i.v.*) pantothenol, for 7 days, did not affect sulphadimidine acetylation kinetics in 21 elderly volunteers (hospital in-patients), as compared with pre-supplementation analyses. No side effects of the therapy were reported (Vas *et al.*, 1990).

59. Nice *et al.* (1984) carried out a double-blind, placebo-controlled trial to investigate the effects of short-term, high-dose pantothenic acid supplementation on exercise performance in 18 trained male distance runners. Participants were divided into 2 groups, one of which was given pantothenic acid supplement of 1 g/day, the other placebo, for 2 weeks. Exercise performance, assessed at the beginning and end of the 2 week period, was not significantly different between the test and placebo groups. The authors reported that there were no significant changes (other than those accounted for by haemoconcentration) in total protein, albumin, calcium, cholesterol, blood urea nitrogen, uric acid, creatinine, bilirubin, alkaline phosphatase, aspartate transaminase, Na^+ , K^+ , Cl^- or HCO_3^- . No side effects of the therapy were reported.

60. In their book – “Overcoming the Pain of Inflammatory Arthritis”, Eisenstein & Scheiner (1997) reported a [non-peer-reviewed] single (patient)-blind, placebo-controlled, crossover trial of high dose pantothenic acid supplementation in a group of 30 subjects with osteo- ($n = 21$) or rheumatoid ($n = 9$) arthritis. Participants were randomised to daily supplementation with either 1.0 g calcium pantothenate, or placebo, for 14 days, followed immediately by 14 days of the opposite treatment. Assessed outcomes were patient-reported symptoms of arthritis severity (pain and stiffness, each recorded daily on a 5-point scale). Supplementation was associated with a significant reduction in pain symptoms in the rheumatoid arthritis group, as compared with pre-treatment, but not placebo-treatment, values. No beneficial effects were determined for the osteoarthritis group. No side effects of the therapy were reported.

61. An open study regarding the potential therapeutic effects of pantothenate supplementation in patients with lupus erythematosus was reported by Cochrane & Leslie (1952). A total of 37 patients was treated with daily doses of ≤ 600 mg calcium pantothenate (in the majority of cases the dose was 400 mg/day) for periods of ≤ 24 weeks. Improvement of disease symptoms was not observed in any of the treated subjects, although some cases worsened during the study period. No side effects of the therapy were reported.

62. In a published abstract, Moiseenok *et al.* (2000) described a study including 156 patients undergoing standard therapeutic treatment for viral hepatitis A. Sub-groups of patients (described as “comparable by clinical state” with control subjects receiving no extra supplementation) were given supplementation comprising 300-600 mg/day calcium pantothenate, or 90-180 mg/day pantothenol, for 3-4 weeks. Treatment with both of these pantothenic acid derivatives was associated with improved immune response, as compared with the control group. No side effects of the therapy were reported.

63. Arnold *et al.* (1978) carried out a randomised, double-blind, placebo-controlled trial to assess the effectiveness of short-term megavitamin therapy in improving behavioural indices in 31 children with “minimal brain dysfunction”. Participants were given supplementation, for 2 weeks, with either a combined vitamin preparation (providing a total daily dose of 400 mg calcium pantothenate, 2 g niacin, 2 g ascorbic acid, 1 g glutamic acid, 200 mg pyridoxine hydrochloride), or placebo. Indices of behaviour were assessed at the beginning and end of the supplementation period. The authors found no significant differences in these measures between the multivitamin and placebo groups. No side effects of the therapy were reported.

64. Goldman (1948) reported that treatment of 14 lupus erythematosus patients with doses of 200-400 mg/day calcium pantothenate (duration not stated) was associated with improvement of the inflammatory phase of the disease, and that “there were no reactions to the therapy”.

65. Brenner (1982) reported a 3-stage trial in which the effectiveness of calcium pantothenate therapy was studied for the treatment of behavioural problems in a total of 100 children with hyperkineses and cerebral dysfunction. *Stage 1* (all participants) comprised 3 days of placebo treatment, a 1-4 day washout period, followed by 3 days of treatment with calcium pantothenate (218 mg/day). Fifteen children who showed a positive response in stage 1 progressed to *stage 2*, which comprised 1 week of calcium pantothenate therapy (218 mg/day), followed by 1 week of placebo treatment. Four children who were noted to respond positively to calcium pantothenate, but not placebo treatment progressed to *stage 3* (mentioned as long-term single or combined vitamin treatment, but not clearly described within the report). Adverse effects of the calcium pantothenate therapy given during this study were not reported.

66. A randomised, double-blind study was carried out to test the efficacy of combined pantothenic/ascorbic acid supplementation in aiding skin wound healing. A group of 49 patients undergoing resection surgery for tattoos was randomised to 21 days supplementation with either pantothenic acid (200 mg/day) + ascorbic acid (1.0 g/day), or placebo. Analyses after 8 days of supplementation showed a significant increase in skin iron, and significant decrease in skin manganese levels associated with active treatment. After 21 days of supplementation, skin magnesium levels and blood thiamine concentrations were significantly higher, whilst skin manganese levels were significantly lower, in the active treatment compared with placebo group. The treatment did not show a direct benefit in improving the wound healing process. Adverse effects of the therapy were not reported (Vaxman *et al.*, 1995).

67. A further study by Vaxman and colleagues also assessed the effects of pantothenic acid/ascorbic acid supplementation on wound healing parameters after resection surgery for tattoo removal. A total of 27 patients was allocated to 2 supplementation groups:

Group 1 ($n = 17$): 200 mg/day pantothenic acid + 1.0 g/day ascorbic acid
 Group 2 ($n = 10$): 900 mg/day pantothenic acid + 3.0 g/day ascorbic acid.

68. Supplementation was given for 21 days following resection, as described previously (Vaxman *et al.*, 1995, paragraph 66). Analysis of trace element levels after 8 (skin analysis) and 21 (scar analysis) days of supplementation showed significantly

increased magnesium and manganese levels in group 2 as compared with group 1 (skin analysis), and significantly increased magnesium, manganese and copper in group 2 as compared with group 1 (scar analysis). There were no direct differences between the groups in the effectiveness of wound healing. Adverse effects of the therapy were not reported (Vaxman *et al.*, 1996).

69. A randomised, double-blind, placebo-controlled trial was undertaken to test the efficacy of combined supplementation with calcium D-pantothenate (200 mg/day) and L-cysteine hydrochloride (120 mg/day), for 12 weeks, in alleviating the symptoms of arthritis in 41 patients with osteoarthritis of the knee (Haslock & Wright, 1971). No significant outcome differences were observed between the active-treatment and placebo groups. Four patients in the active treatment group withdrew from the trial because of side-effects of headache, sleepiness, depression, memory loss, flatulence and abdominal pain (one subject withdrew from the placebo group – reasons were not stated). These symptoms have not been seen consistently in other reports of pantothenate supplementation, and it is perhaps significant that the patients were also receiving L-cysteine.

70. Annand (1962) reported an open study of 12.5 mg/day pantothenic acid therapy in 26 patients with “worn joint” osteoarthritis. The author stated that cases were treated over a period of 18 months; however, individual or average treatment durations were not described within this report. A reduction in the severity of symptoms of arthritis was reported by 77% of patients. Three subjects reported the gradual development of general asthenia and “leg-weariness”, recovering when 12.5 mg/day pyridoxin therapy was substituted for the pantothenic acid therapy (the author suggested that “a vitamin imbalance may have been at fault in these cases”).

71. A body of literature exists regarding studies of pantothenic acid, including some human supplementation studies, published in languages other than English (mostly in Russian or German). These publications have not been included within this report.

Vulnerable groups

72. Subgroups of the population specifically vulnerable to adverse effects of excess pantothenic acid intake have not been identified.

Genetic variation

73. Genotypes leading to a predisposition for increased susceptibility to adverse effects of pantothenic acid supplementation have not been identified.

Adverse drug reactions

74. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable “under-reporting” of reactions. Very few adverse reactions have been reported for

products containing pantothenic acid. As all reactions relate to multiconstituent products, they may not be directly attributable to the vitamin.

Animal toxicity

75. The limited data that are available indicate very low toxicity of pantothenic acid, and its commonly used pharmacological forms, in experimental animals.

Acute toxicity

76. Unna & Greslin (1940, 1941) reported acute toxicity tests of synthetic D-calcium pantothenate in mice, rats, dogs and a monkey (strains not specified). LD₅₀ values for the compound by various methods of application in mice and rats are summarised in Table 2. Rats dosed with 10 g/kg bw orally survived without showing toxic signs. Lethal doses produced death by respiratory failure, within 2 hours following i.v. and i.p. injection, and within 6-12 hours following oral (mice) and s.c. administration. No late deaths were observed. An oral dose of 1 g/kg bw calcium pantothenate produced no toxic signs in dogs (n = 5) or monkey (n = 1). Examination of one dog and the monkey upon killing after 2 weeks did not show any pathologic changes.

Sub-chronic/ chronic toxicity

Enteral administration

77. Unna & Greslin (1940, 1941) also reported chronic toxicity studies of D-calcium pantothenate in rats, dogs and monkeys (strains not specified). Young male and female rats (10 males and 10 females per group) were fed doses of 50 or 200 mg/day (\approx 500 or 2000 mg/kg bw/day) D-calcium pantothenate, for 190 days. Growth and development were normal and did not differ significantly from those of a control group fed a standard diet. The authors reported that autopsies at the end of the feeding period did not reveal any gross or microscopic changes in the organs (not specified). Six adult dogs and 4 monkeys were fed 50 mg/kg bw/day and 1 g/day (\approx 200-250 mg/kg bw/day) D-calcium pantothenate, respectively, for periods of 6 months. None of the animals showed any toxic signs, or weight loss, during the supplementation period, and again the authors reported that histopathological examination at the end of the supplementation period did not reveal any changes (no details provided).

78. Slyshenkov *et al.* (1998) reported that prior treatment of rats with intragastric doses of panthenol protected the animals against some of the deleterious effects of gamma irradiation. Female albino rats (5 animals per group), fed standard laboratory diets, were given 26 mg/kg bw/day D-panthenol, *via* stomach catheter, for 2 days prior to gamma irradiation. This procedure was repeated three times, at one week intervals, after which the animals were killed and blood and liver analyses were performed. Control groups (\pm gamma irradiation) were not treated with panthenol. Gamma irradiation was associated with significantly reduced total lipid, phospholipid and cholesterol, glutathione and CoA levels, and increased markers of lipid peroxidation and NAD⁺/NADH ratio in the livers of unsupplemented animals. However, within the D-panthenol-treated group, none of these indices showed significant differences from the non-irradiated control group, indicating a protective

effect of panthenol treatment against gamma irradiation. No adverse effects of the panthenol treatment were described.

79. In a study to assess the effects of pantothenic acid supplementation on longevity, 33 young (male and female) C-57 black mice were supplemented with approximately 0.3 mg/day (\approx 15 mg/kg bw/day) calcium pantothenate in the drinking water, for life. Forty one control mice did not receive the supplement. Comparison of same-sex groups showed approximately 20% increased lifespan associated with pantothenic acid treatment (mean life spans were \approx 550 and 650 days, for control and supplemented animals, respectively). Treated animals also showed slightly increased body weights, as compared with the control group, from \approx 250 days onwards (Pelton & Williams, 1958).

Parenteral administration

80. Nagiel-Ostaszewski & Lau-Cam (1990) reported that i.p. administration of D-pantothenic acid (100 mg/kg bw/day) or D-pantethine (500 mg/kg bw/day), for 5 days, conferred significant protection against the hepatotoxic and peroxidative actions of carbon tetrachloride in male Sprague-Dawley rats ($n = 6$ per group). Pantethine or pantothenic acid – only groups (without CCl₄ treatment) were not included.

81. Aprahamian *et al.* (1985) reported that treatment of rabbits (Chinchilla pure breed) ($n = 12$) with pantothenic acid (20 mg/kg bw, by “injection”, for 3 weeks pre- and 30 days post-operatively) improved some parameters of skin wound healing, as compared with animals fed diets containing control ($n = 30$ [of which a sub-group of 18 animals received placebo injections of saline]) or deficient ($n = 12$) levels of pantothenic acid.

82. Sonmez *et al.* (2000) assessed the effects of pantothenic acid treatment on adhesion formation following uterine lesion, in eu-oestrogenic and hypo-oestrogenic female Sprague-Dawley rats. Six groups of 5 animals were treated with pantothenic acid (63-70 mg *i.p.* during surgery, or 20 mg/kg bw/day *i.m.* for 7 days after surgery), or saline (control). The authors reported that no animals suffered complications or side effects related to pantothenic acid (2 animals died due to complications of anaesthesia, one in each of the hypo-oestrogenic saline and hypo-oestrogenic *i.p.* pantothenic acid groups). Pantothenic acid treatment was not associated with reduced incidence of adhesions.

Neurotoxicity

83. No data were identified regarding neurotoxic effects of pantothenic acid, or its commonly-used pharmaceutical forms, in experimental animals.

Carcinogenicity

84. No data were identified regarding carcinogenic effects of pantothenic acid, or its commonly-used pharmaceutical forms, in experimental animals.

Genotoxicity

In vitro

85. Calcium pantothenate (CAS: 137-08-6) was not mutagenic in the Ames *S. typhimurium* test, strains TA97, TA102 (0.1-10 mg/plate, with or without metabolic activation) (Fujita & Sasaki, 1987, cited by CCRIS database, accessed at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS>, November 2000).

86. Sivak & Tu (1980) reported that calcium pantothenate (2.1×10^{-3} M) enhanced both spontaneous and 3-methylcholantrene-induced transformation in BALB/c-3T3 cells *in vitro*, although these effects were only noted in one set of identical (duplicate) experiments described within the same report.

87. Sodium pantothenate (CAS: 867-81-2) was not mutagenic in the Ames *S. typhimurium* test, strains TA97, TA102 (0.1-10 mg/plate, with or without metabolic activation) (Fujita & Sasaki, 1986, cited by CCRIS database, accessed at <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS>, November 2000).

88. D-Pantothenyl alcohol (panthenol) (CAS: 81-13-0) was not mutagenic in the Ames *S. typhimurium* test, strains TA98, TA100, TA1535, TA1537, TA1537, or *E. coli* strain WP2, (0.033-10 mg/plate, with or without metabolic activation) (Prival *et al.*, 1991).

In vivo

89. Reports regarding *in vivo* genotoxicity testing of pantothenic acid and its commonly available pharmaceutical forms have not been found.

Reproductive toxicity

90. Young rats (10 male, 10 female, strain not specified) were fed 50 mg/day (\approx 500 mg/kg bw/day) calcium pantothenate for 190 days with no adverse effects (see paragraph 76). The offspring of this group (4 male, 6 female) were also fed 50 mg/day calcium pantothenate from weaning. The authors reported that these animals developed normally, their weights increased at the same rate as those of a control group and that histopathological examination of all animals at termination did not reveal any changes (Unna & Gresli, 1941).

91. A small number of studies have assessed the effects of supplementation with pantothenic acid compounds on valproic acid-induced teratogenesis in experimental animals.

92. Sato *et al.* (1995) reported that i.p. injection of calcium pantothenate solution in ICR mice on day 8.5 of gestation (3 dose regimes:- 3 x 10 mg/kg bw [$n = 7$]; 3 x 100 mg/kg bw [$n = 12$]; 3 x 300 mg/kg bw [$n = 15$]) showed no effects of maternal toxicity, embryotoxicity (embryo viability, average number of live foetuses per litter), or teratogenicity, as compared with a control group of 28 dams given injected with saline. Co-administration of calcium pantothenate (3 x 300 mg/kg bw) with valproic acid (VPA) (300, 400 or 500 mg/kg bw) was associated with a significant reduction of

VPA-induced foetal exencephaly (neural tube defects – NTDs), as compared with VPA-treatment alone.

93. A recent report by Bennett *et al.* (1998 [published abstract]) also described a reduction of VPA-induced NTDs associated with daily treatment of pregnant LMBc mouse dams (numbers not stated) with pantothenic acid (100 mg/kg bw/day – probably by i.p. injection, although the route of application was not clearly stated) during gestation days 6.5-10.5. Conversely, similar treatment using a higher dose of pantothenic acid (300 mg/kg bw/day) was associated with a significant increase in VPA-induced NTDs. Further details of this study were not provided.

94. A study in which Sprague-Dawley rat embryos were cultured with or without 1 mg/ml pantothenic acid prior to treatment with 0.9 mM VPA, showed no significant effect of pantothenic acid on the incidence of VPA-induced NTDs (incidence = 67% VPA; 56% VPA/pantothenic acid) (Grafton *et al.*, 1997 [published abstract]).

Mechanisms of toxicity

95. Not applicable.

Regulatory considerations

96. The Recommended Daily Allowance in the Food Labelling Regulations for pantothenic acid is 6mg. The Infant Formula and Follow-on Formula Regulations (1995) recommend a minimum pantothenic acid content of 300 µg/100 kcal. The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations (1999) recommend a maximum pantothenic acid content of 1.5 mg/100 kcal. The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations (1997) recommend that whole diet products should provide 3mg and meal replacements 0.9mg.

Existing recommendations on maximum intake levels

97. No data identified.

Existing recommendations on maximum supplementation levels

98. The Committee on Medical Aspects of Food and Nutrition Policy reported that there were no toxic signs after giving adult men 10 g calcium pantothenate for 6 weeks, although such doses may cause diarrhoea and gastrointestinal disturbances (DH 1991).

99. The Council for Responsible Nutrition, a UK trade association recommends a Upper Safe Level of 1000 mg/day pantothenic acid for both long and short term supplementation, noting that no adverse effect has been identified (CRN, 1999). Shrimpton (1995) recommends a maximum supplementation level of 500 mg/day.

Summary

100. Pantothenic acid (vitamin B₅) is a water-soluble vitamin of the B-complex which is present in virtually all living cells. The compound, which is usually present in the form of coenzyme A (CoA)-containing species, performs multiple roles within cellular metabolism and in the synthesis of many essential molecules.

101. Pure pantothenic acid exists as a yellow viscous oil, which is unstable to acids, bases and heat. Within foods, the majority of the compound exists as a component of CoA. Data regarding the absolute levels of pantothenic acid content in foods are limited by methods of analysis. However, chicken, beef, potatoes, oat cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli and whole grains are reported to be major sources of the vitamin, whilst very high levels are present in royal bee jelly and in the ovaries of tuna and cod. Dietary supplements and pharmaceutical forms of pantothenic acid are generally available as calcium pantothenate or panthenol (as the biologically-active D-enantiomer), which are rapidly converted to the free acid within the body. Pantothenic acid within natural foods has been reported as approximately 50% bioavailable compared with pure calcium pantothenate given in a formula diet.

102. In humans, pantothenic acid requirements are provided by the diet, with mean intakes (from food) in the UK of 4.5 and 6.3 mg/day, for women and men, respectively. (Synthesis by intestinal microflora occurs in ruminants, and has also been noted in mice, but the potential contribution of this source of the vitamin in humans has not been reported). Dietary reference values for pantothenic acid have not been established. However, standard intakes between 3 and 7 mg/day are assumed to be adequate, as signs of deficiency are not observed within the general population.

103. Ingested CoA is hydrolysed within the intestinal lumen, *via* the formation of dephospho-CoA, phosphopantetheine and pantetheine, to pantothenic acid. Uptake of these latter two compounds into intestinal tissues has been demonstrated in rats, whereupon the enzyme, pantetheinase, can hydrolyse pantetheine to pantothenic acid. Absorption of pantothenate into intestinal cells occurs readily by both a sodium-dependent active transport mechanism and by passive diffusion. Absorbed pantothenic acid is transported to body tissues via the blood, primarily as bound forms within erythrocytes. Plasma levels do not correlate well with dietary intake. The majority of tissues import pantothenic acid via an active sodium cotransport mechanism. Recent molecular studies have suggested that this uptake mechanism may be shared with biotin and other molecules, although the physiological importance of this is not known. Within cells, CoA is synthesised from pantothenic acid, with the first, and apparently rate-limiting, step catalysed by pantothenate kinase. Catabolism of CoA leads to the formation of pantothenate, which is excreted in the urine. Excretion levels are reported to correlate well with dietary intake.

104. Deficiency of pantothenic acid in humans is extremely rare, presumably because the compound is so widely present within foods. Blood pantothenic acid levels have been reported to be low in patients with rheumatoid arthritis, and some reports suggest beneficial effects of supplementation in these subjects, as well as in patients with lupus erythematosus. However, these claims have not been widely tested in large-scale, controlled human studies. Studies using animal models have indicated

non-nutritional beneficial effects of pantothenic acid, such as protection against carbon tetrachloride and radiation damage.

105. Pantothenic acid supplementation is generally considered as safe, even at extremely high doses, as excesses of the compound are mostly excreted in the urine, rather than being stored in the tissues. Case reports and some rather old, uncontrolled studies describe a lack of acute or chronic toxic effects of pantothenic acid compounds (calcium or sodium pantothenate, panthenol) at very high doses (≈ 10 g/day, in some cases, apparently for a number of years), although such levels have been associated with diarrhoea and gastrointestinal disturbances. More recent, controlled studies (generally carried out to assess the potential benefits of pantothenic acid supplementation in specific subgroups – for example, arthritic patients) have reported no adverse effects at levels up to ≈ 2 g/day, for periods of several days to several weeks. However, the small numbers of participants and short duration of these studies limit data regarding any potential rare or long-term toxic effects.

106. One open-design trial, carried out to investigate the effectiveness of megavitamin therapy in improving the behaviour of 41 children with attention deficit disorders, showed significant increases in serum aspartate transaminase levels in 17 children after 12 weeks of multivitamin therapy (including doses of calcium pantothenate increasing during the study period a maximum of 1.2 g/day). This effect was considered most likely to be associated with the niacinamide component of the multivitamin supplement, although this could not be confirmed as vitamins were not given separately.

107. No data are available to suggest that specific subgroups of the population, or those with particular genotypes, may be especially susceptible to pantothenic acid toxicity.

108. Data regarding toxicity testing of pantothenic acid and its commonly-used pharmaceutical forms in experimental animals are also limited. In the early 1940's Unna & Greslin reported acute and chronic toxicity tests with D-calcium pantothenate in mice, rats, dogs and monkeys. Acute oral LD₅₀ values were very high (≥ 10 g/kg bw, mice and rats), with lethal doses producing death by respiratory failure. An oral dose of 1 g/kg bw produced no toxic signs in dogs ($n = 5$) or monkey ($n = 1$). Chronic oral dosing (500 or 2000 mg/kg bw/day – rats [$n = 20$ per dosage group]; 50 mg/kg bw/day – dogs [$n = 6$]; 200-250 mg/kg bw/day – monkeys [$n = 4$]) for 6 months also produced no toxic signs or weight loss during supplementation, nor evidence of histopathological changes at autopsy. The offspring of rats supplemented with 500 mg/kg bw/day calcium pantothenate were fed the same dose from weaning, with no evidence of toxicity, reduced weight gain or histopathological changes.

109. Calcium pantothenate, sodium pantothenate and panthenol were not mutagenic to bacteria.

REFERENCES

- Annand, J.C. (1962). Osteoarthritis and pantothenic acid. *Journal of the College of General Practitioners*, **5**, 136-137.
- Aprahamian, M., Dentinger, A., Stock-Damge, C. *et al.* (1985). Effects of supplemental pantothenic acid on wound healing: experimental study in rabbit. *American Journal of Clinical Nutrition*, **41**, 578-589.
- Arnold, L.E., Christopher, J., Huestis, R.D., Smeltzer, D.J. (1978). Megavitamins for minimal brain dysfunction. A placebo-controlled study. *Journal of the American Medical Association*, **240**, 2642-2643.
- Baggot, P.J., Kalamarides, J.A., Shoemaker, J.D. (1999). Valproate-induced biochemical abnormalities in pregnancy corrected by vitamins: a case report. *Epilepsia*, **40**, 512-515.
- Baker, H., Frank, O., Thomson, A.D., Feingold, S. (1969). Vitamin distribution in red blood cells, plasma and other body fluids. *American Journal of Clinical Nutrition*, **22**, 1469-1475.
- Barbarat, B., Podevin, R.A. (1986). Pantothenate-sodium cotransport in renal brush-border membranes. *J. Biol. Chem.*, **261**, 14455-14460.
- Barboriak, J.J., Krehl, W.A. (1957). Effect of ascorbic acid in pantothenic acid deficiency. *Journal of Nutrition*, **63**, 601-609.
- Barton-Wright, E.C., Elliott, W.A. (1963). The pantothenic acid metabolism of rheumatoid arthritis. *Lancet*, Oct. 26, 862-863.
- Beinlich, C.J., Naumovitz, R.D., Song, W.O., Neely, J.R. (1990). Myocardial metabolism of pantothenic acid in chronically diabetic rats. *J. Mol. Cell. Cardiol.*, **22**, 323-332.
- Bender, D.A., Bender, A.E. (1997). Nutrition: a reference handbook. Oxford University Press Oxford, UK.
- Bender, D. A. (1999) Optimum nutrition: thiamin, biotin and pantothenate. *Proceedings of the Nutrition Society*, **58**, 427-433.
- Bennett, G.D., Ridge, L., Finnell, R.H. (1998). Folate, vitamin B₁₂, inositol or pantothenic acid supplementation exacerbates the frequency of valproic acid induced neural tube defects. *Toxicologist*, **42**(1-S), 262 (Abstract).
- van den Berg, H. (1997). Bioavailability of pantothenic acid. *Eur. J. Clin. Nutr.*, **51**, S62-S63.
- Brenner, A. (1982). The effects of megadoses of selected B complex vitamins on children with hyperkinesia: controlled studies with long-term follow-up. *J. Learn. Disabil.*, **15**, 258-264.

Chatterjee, N.S., Kumar, C.K., Ortiz, A. *et al.* (1999). Molecular mechanism of the intestinal biotin transport process. *Am. J. Physiol.*, **277**, C605-C613.

Cochrane, T., Leslie, G. (1952). The treatment of lupus erythematosus with calcium pantothenate and panthenol. *J. Invest. Dermat.*, **18**, 365-367.

CRN (1999). The safe use of supplements benefits good health. The Council for Responsible Nutrition. (leaflet).

Department of Health (1991). Pantothenic acid. *In: Dietary reference values for food, energy and nutrients for the United Kingdom: Report of the panel on dietary reference values of the committee on medical aspects of food policy.* HMSO, London, pp. 113-115.

Eisenstein, P., Scheiner, S.A. (1997). Overcoming the pain of inflammatory arthritis: the pain-free promise of pantothenic acid. Avery Publishing Group, Garden City Park, New York.

Eissenstat, B.R., Wyse, B.W., Hansen, R.G. (1986). Pantothenic acid status of adolescents. *American Journal of Clinical Nutrition*, **44**, 931-937.

Even, P.C., Decrouy, A., Chinet A. (1994). Defective regulation of energy metabolism in mdx-mouse skeletal muscles. *Biochem., J.*, **304**, 649-654.

Everson, G., Northrop, L., Chung, N.Y., Getty, R. (1954). Effect of ascorbic acid on rats deprived of pantothenic acid during pregnancy. *J. Nutr.*, **54**, 305-311.

Fenstermacher, D.K., Rose, R.C. (1986). Absorption of pantothenic acid in rat and chick intestine. *Am. J. Physiol.*, **250**, G155-G160.

Food and Nutrition Board – Institute of Medicine. (2000). Dietary reference intakes. Thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. National Academy Press, Washington DC.

Fox, H.M. (1984). *In: Handbook of Vitamins: Nutritional, Biochemical and Clinical Aspects*, Machlin, L.J. (ed.), Marcel Dekker, NY, pp. 437-457.

Fry, P.C., Fox, H.M., Tao, H.G. (1976). Metabolic response to a pantothenic acid deficient diet in humans. *J. Nutr. Sci. Vitaminol.* (Tokyo), **22**, 339-346.

General Practitioner Research Group (1980). Calcium pantothenate in arthritic conditions. A report from the General Practitioner Research Group. *Practitioner*, **224**, 208-211.

Glusman, M. (1947). The syndrome of “burning feet” (nutritional melalgia) as a manifestation of nutritional deficiency. *Am. J. Med.*, **3**, 211-223.

Goldman, L. (1948). Treatment of subacute and chronic discoid lupus erythematosus with intensive calcium pantothenate therapy. *J. Invest. Dermat.*, **11**, 95.

- Goldman, L. (1950). Intensive pantothenol therapy of lupus erythematosus. *J. Invest. Dermat.*, **15**, 291-293.
- Grafton, T.F., Dial, S.L., Hansen, D.K. (1997). Lack of amelioration of valproic acid-induced embryotoxicity by pantothenic acid in vitro. *Teratology*, **55**, 58 (ABSTRACT).
- Grassl, S.M. (1992). Human placental brush-border membrane Na⁺-pantothenate cotransport. *J. Biol. Chem.*, **267**, 22902-22906.
- Gregory, J.R., Foster, K., Tyler, H., Wiseman, M. (1990). The Dietary and Nutritional Survey of British Adults, HMSO, London.
- Haslam, R.H., Dalby, J.T., Rademaker, A.W. (1984). Effects of megavitamin therapy on children with attention deficit disorders. *Pediatrics*, **74**, 103-111.
- Haslock, D.I., Wright, V. (1971). Pantothenic acid in the treatment of osteoarthritis. *Rheumatology and Physical Medicine*, **11**, 10-13.
- Hatano, M., Hodges, R.E., Evans, T.C. *et al.* (1967). Urinary excretion of pantothenic acid by diabetic patients and by alloxan-diabetic rats. *American Journal of Clinical Nutrition*, **20**, 960-967.
- Hodges, R.E., Ohlson, M.A., Bean, W.B. (1958). Pantothenic acid deficiency in man. *J. Clin. Invest.*, **37**, 1642-1657.
- Hodges, R.E., Bean, W.B., Ohlson, M.A., Bleiler, R. (1959). Human pantothenic acid deficiency produced by omega-methyl pantothenic acid. *J. Clin. Invest.*, **38**, 1421-1425.
- Johnston, L., Vaughan, L., Fox, H.M. (1981). Pantothenic acid content of human milk. *American Journal of Clinical Nutrition*, **34**, 2205-2209.
- Kapp, A., Zeck-Kapp, G. (1991). Effect of Ca-pantothenate on human granulocyte oxidative metabolism. *Allerg. Immunol.*, **37**, 145-150.
- Kimura, S., Furukawa, Y., Wakasugi, J. *et al.* (1980). Antagonism of L(-)pantothenic acid on lipid metabolism in animals. *J. Nutr. Sci. Vitaminol.* (Tokyo), **26**, 113-117.
- Koyanagi, T., Hareyama, S., Kikuchi, R. *et al.* (1969). Effect of administration of thiamine, riboflavin, ascorbic acid and vitamin A to students on their pantothenic acid contents in serum and urine. *Tohoku J. Exp. Med.*, **98**, 357-362.
- Lacroix, B., Didier, E., Grenier, J.F. (1988). Role of pantothenic and ascorbic acid in wound healing processes: in vitro study on fibroblasts. *Int. J. Vitam. Nutr. Res.*, **58**, 407-413.

Latymer, E.A., Coates, M.E. (1981). The effects of high dietary supplements of copper sulphate on pantothenic acid metabolism in the chick. *British Journal of Nutrition*, **45**, 431-439.

Lewis, C.M., King, J.C. (1980). Effect of oral contraceptive agents on thiamin, riboflavin, and pantothenic acid status in young women. *American Journal of Clinical Nutrition*, **33**, 832-838.

Litoff, D., Scherzer, H., Harrison, J. (1985). Effects of pantothenic acid supplementation on human exercise. *Med. Sci. Sport. Exerc.*, **17** [Suppl.], 287.

Lopaschuk, G.D., Michalak, M., Tsang, H. (1987). Regulation of pantothenic acid transport in the heart. Involvement of a Na⁺-cotransport system. *J. Biol. Chem.*, **262**, 3615-3619.

Luecke, R.W., Hoefler, J.A., Thorp, F. Jr. (1952). The relationship of protein to pantothenic acid and vitamin B₁₂ in the growing pig. *J. Anim. Sci.*, **11**, 238-243.

McKiernan, S.H. and Bavister, B.D. (2000). Culture of one-cell hamster embryos with water soluble vitamins: pantothenate stimulates blastocyst production. *Hum. Reprod.* **15**, 157-164

Moiseenok, A.G., Komar, V.I., Khomich, T.I. *et al.* (2000). Pantothenic acid in maintaining thiol and immune homeostasis. *Biofactors*, **11**, 53-55.

Nagiel-Ostaszewski, I., Lau-Cam, C.A. (1990). Protection by pantethine, pantothenic acid and cystamine against carbon tetrachloride-induced hepatotoxicity in the rat. *Res. Commun. Chem. Pathol. Pharmacol.*, **67**, 289-292.

Nelson, M.M., Evans, H.M. (1945). Sparing action of protein on the pantothenic acid requirement of the rat. *Proc. Soc. Exp. Biol. Med.*, **60**, 319-320.

Nice, C., Reeves, A.G., Brinck-Johnsen, T., Noll, W. (1984). The effects of pantothenic acid on human exercise capacity. *J. Sports Med. Phys. Fitness*, **24**, 26-29.

Okuda, K., McCollum, E.B., Hsu, J.M., Chow, B.F. (1962). Utilization of vitamin B₁₂ by rats with pantothenic acid deficiency. *Proc. Soc. Exp. Biol. Med.*, **111**, 300-304.

Ono, S., Kameda, K., Abiko, Y. (1974). Metabolism of pantetheine in the rat. *J. Nutr. Sci. Vitaminol.*, **20**, 203-213.

OTC (2001). OTC Directory 2001-2002, Proprietary Association of Great Britain.

Otsuka, M., Akiba, T., Okita, Y. *et al.* (1990). Lactic acidosis with hypoglycaemia and hyperammonemia observed in two uremic patients during calcium hopantenate treatment. *Jpn. J. Med.*, **29**, 324-328.

Palekar, A. (2000). Effect of pantothenic acid on hippurate formation in sodium benzoate-treated HepG2 cells. *Pediatr. Res.*, **48**, 357-359.

Pelton, R.B., Williams, R.J. (1958). Effect of pantothenic acid on the longevity of mice. *Proc. Soc. Exp. Biol. Med.*, **99**, 632-633.

Plesofsky-Vig, N. (1999). Pantothenic acid. In: *Modern Nutrition in Health and Disease*, 9th ed., Shils, M.E., Olson, J.A., Shike, M., Ross, A.C. (eds), Williams & Wilkins, Baltimore, pp. 423-432.

Prasad, P.D., Ramamoorthy, S., Leibach, F.H., Ganapathy, V. (1997). Characterisation of a sodium-dependent vitamin transporter mediating the uptake of pantothenate, biotin and lipoate in human placental choriocarcinoma cells. *Placenta* **18**, 527-33.

Prasad, P.D., Srinivas, S.R., Wang, H. *et al.* (1999). Electrogenic nature of rat sodium-dependent multivitamin transport. *Biochem. Biophys. Res. Comm.*, **270**, 836-840.

Prival, M.J., Simmon, V.F., Mortelmans, K.E. (1991). Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. *Mutat. Res.*, **260**, 321-329.

Pudlakewicz, C., Roderuck, C. (1960). Pantothenic acid deficiency in the young guinea pig. *J. Nutr.*, **70**, 348-352.

Ralli, E.P. (1952). The effect of certain nutritional factors on the reactions produced by acute stress in human subjects. *National Vitamin Foundation Nutrition Symposium*, **5**, 78-103.

Reibel, D.K., Wyse, B.W., Berkich, D.A. *et al.* (1981). Effects of diabetes and fasting on pantothenic acid metabolism in rats. *Am. J. Physiol.*, **240**, E597-E601.

Robishaw, J.D., Berkich, D., Neely, J.R. (1982). Rate-limiting step and control of coenzyme A synthesis in cardiac muscle. *J. Biol. Chem.*, **257**, 10967-10972.

Robinson, F.A. (1966). *The vitamin co-factors of enzyme systems*. Pergamon Press, Oxford, pp. 406-486.

Said, H.M., Ortiz, A., McCloud, E. *et al.* (1998). Biotin uptake by human colonic epithelial NCM460 cells: a carrier-mediated process shared with pantothenic acid. *Am. J. Physiol.*, **275**: 5 pt 1, C1365-1371

Said, H.M. (1999). Cellular uptake of biotin: mechanisms and regulation. *J. Nutr.*, **129**, 490S-493S

Sato, M., Shirota, M., Nagao, T. (1995). Pantothenic acid decreases valproic acid-induced neural tube defects in mice (I). *Teratology*, **52**, 143-148.

Schroeder, H.A. (1971). Losses of vitamins and trace minerals resulting from processing and preservation of foods. *American Journal of Clinical Nutrition*, **24**, 562-573.

Sewell, R.F., Price, D.G., Thomas, M.C. (1962). Pantothenic acid requirement of the pig as influenced by dietary fat. *Fed. Proc.*, **21**, 468.

Shibata, K., Gross, C.J., Henderson, L.M. (1983). Hydrolysis and absorption of pantothenate and its coenzymes in the rat small intestine. *Journal of Nutrition*, **113**, 2107-2115.

Shrimpton, D (1995). Essential Nutrients in Supplements. European Federation of Associations of Health Product Manufacturers.

Sivak, A., Tu, A.S. (1980). Cell culture tumor promotion experiments with saccharin, phorbol myristate acetate and several common food materials. *Cancer Letters*, **10**, 27-32.

Slyshenkov, V.S., Omelyanchik, S.N., Moiseenok, A.G. *et al.* (1998). Pantothenol protects rats against some deleterious effects of gamma radiation. *Free Radic. Biol. Med.*, **24**, 894-899.

Song, W.O., Wyse, B.W., Hansen, R.G. (1985). Pantothenic acid status of pregnant and lactating women. *J. Am. Diet. Assoc.*, **85**, 192-198.

Sonmez, A., Lurie, D., Chuong, C.J. (2000). Effects of pantothenic acid on postoperative adhesion formation in a rat uterine horn model. *Arch. Gynecol. Obstet.*, **263**, 164-167.

Spector, R., Mock, D. (1987). Biotin transport through the blood-brain barrier. *J. Neurochem.*, **48**, 400-404.

Srinivasan, V., Christensen, N., Wyse, B.W., Hansen, R.G. (1981). Pantothenic acid nutritional status in the elderly-institutionalized and non-institutionalized. *Am. J. Clin. Nutr.*, **34**, 1736-1742.

Stein, E.D., Diamonds, J.M. (1989). Do dietary levels of pantothenic acid regulate its intestinal uptake in mice? *J. Nutr.*, **119**, 1973-1983.

Tahiliani, A.G., Beinlich, C.H. (1991). Pantothenic acid in health and disease. *Vitam. Horm.*, **46**, 165-228.

Tao, H.G., Fox, H.M. (1976). Protein-pantothenic acid interrelationships in growing rats. *Nutr. Rep. Int.*, **14**, 97-106.

Tarr, J.B., Tamura, T., Stokstad, E.L. (1981). Availability of vitamin B₆ and pantothenate in an average American diet in man. *Am. J. Clin. Nutr.*, **33**, 1328-1337.

Unna, K. Greslin, J.G. (1940). Toxicity of pantothenic acid. *Proc. Soc. Exp. Biol. Med.*, **45**, 311-312.

Unna, K., Greslin, J.G. (1941). Studies on the toxicity and pharmacology of pantothenic acid. *J. Pharmacol. Exp. Ther.*, **73**, 85-90.

Vas, A., Gachalyi, B., Kaldor, A. (1990). Pantothenic acid, acute ethanol consumption and sulphadimidine acetylation. *Int. J. Clin. Pharmacol. Ther. Toxicol.*, 28, 111-114.

Vaxman, F., Olender, S., Lambert, A. *et al.* (1995). Effect of pantothenic acid and ascorbic acid supplementation on human skin wound healing process. A double-blind, prospective and randomized trial. *Eur. Surg. Res.*, 27, 158-166.

Vaxman, F., Olender, S., Lambert, A. *et al.* (1996). Can the wound healing process be improved by vitamin supplementation? Experimental study on humans. *Eur. Surg. Res.*, 28, 306-314.

Walsh, J.H., Wyse, B.W., Hansen R.G. (1981). Pantothenic acid content of 75 processed and cooked foods. *J. Am. Diet. Assoc.*, 78, 140-144.

Wang, H., Huang, W., Fei, Y.J. *et al.* (1999). Human placental Na⁺-dependent multivitamin transporter. Cloning, functional expression, gene structure, and chromosomal localization. *J. Biol. Chem.*, 274, 14875-14883.

Webster, M.J. (1998). Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. *Eur. J. Appl. Physiol. Occup. Physiol.*, 77, 486-491.

Welsh, A.L. (1952). Lupus erythematosus: treatment by combined use of massive amounts of calcium pantothenate or panthenol with synthetic vitamin E. *Arch. Dermat., Syph.*, 65, 137-148.

Welsh, A.L. (1954). Lupus erythematosus: treatment by combined use of massive amounts of pantothenic acid and vitamin E. *Archives of Dermatology*, 70, 181-198.

Wittwer, C.T., Gahl, W.A., Butler, J. deB. *et al.* (1985). Metabolism of pantethine in cystinosis. *J. Clin. Invest.*, 76, 1665-1672.

Wittwer, C.T., Burkhard, D., Ririe, K. (1983). Purification and properties of a pantetheine-hydrolyzing enzyme from pig kidney. *J. Biol. Chem.*, 257, 9733-9738.

Yacowitz, H., Norris, L.C., Heuse, G.F. (1951). Evidence for an interrelationship between vitamin B₁₂ and pantothenic acid. *J. Biol. Chem.*, 192, 141-146.

ANNEX 1 TO EVM/01/01

Tables and figures referred to in the review

Figure 1. Coenzyme A and intermediates.

Figure 2. Pathway for the conversion of pantothenic acid to coenzyme A (adapted from Fox, 1984).

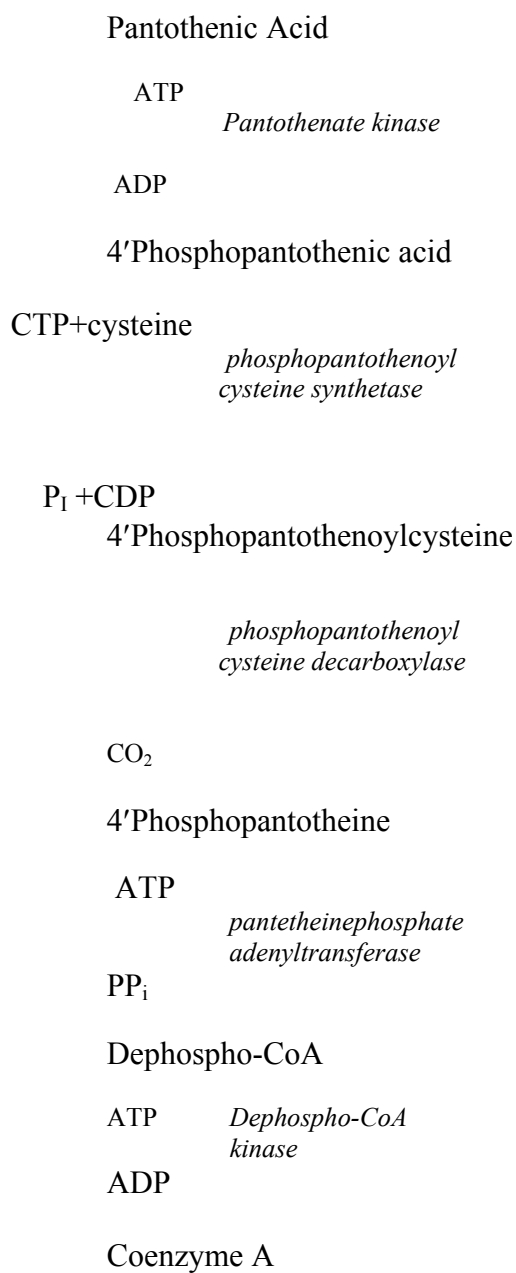


Table 1. Pantothenic acid supplementation studies in humans.

Reference	Subjects	n	Study aim	Study design	Daily dose(s) of pantothenic acid compound	Formulation	Duration of treatment	Comments
Welsh (1952, 1954)	Patients with lupus erythematosus	67	Treatment of the symptoms of lupus erythematosus	Open	5-15 g (???) (+ 1-2 g vitamin E derivatives)	Calcium pantothenate (10-15 g/day); Pantothenyl alcohol (10-15 g/day); Sodium pantothenate (5-10 g/day)	Up to 3 years	Transient nausea and gastric distress in a few patients. Normal haematological and urinary analyses in patients maintained on the therapy for 1-3 years.
Ralli (1952)	Adult men	12	To assess the effects of supplementation on response to cold water stress	Open	10 g	Calcium pantothenate	6 weeks	The authors reported the following differences in urinary/blood tests following cold-water stress associated with pantothenic acid therapy, as compared with equivalent testing performed prior to therapy; reduced eosinophilic response and less variation in the response of white blood cells; significantly reduced serum chloride values; significantly increased blood ascorbic acid concentrations and increased urinary ascorbic acid excretion; significantly decreased uric acid/creatinine ratio; No side effects of the therapy were reported.
Goldman (1950)	Patients with lupus erythematosus	19	Treatment of the symptoms of lupus erythematosus	Open	Various doses, up to 10 g/day	Panthenol	Several weeks to several months	Improvement in some subjects; The authors reported that "There is apparently no toxicity of panthenol even at dosage levels of 8-10 grams daily. Patients have been maintained on 1 and 2 grams daily for as long as six months." Three patients died, but the authors did not associate this with panthenol therapy.

General Practitioner Research Group (1980)	Patients with a diagnosis of arthritis (osteoarthritis, rheumatoid arthritis, gout, spondylitis, psoriatic arthritis, one patient not-specified)	94	Treatment of the symptoms of arthritis	Randomised, double-blind, placebo-controlled	Days 1-2: 0.5 g Days 3-5: 1.0 g Days 6-9: 1.5 g Day 10- : 2.0 g	Calcium pantothenate	8 weeks	Supplementation was associated with a significant reduction of some patient-reported symptoms in the rheumatoid arthritis sub-group, but not in the study group as a whole. No side effects were recorded in 43 (91%) and 37 (79%) patients in the active treatment and placebo groups, respectively
Litoff <i>et al.</i> (1985)	Trained, male runners	7	Assessment of the effects of supplementation on parameters of exercise capacity	Randomised, double-blind, placebo-controlled, crossover	2 g	Pantothenic acid	14 days	Active treatment was associated with decreased blood lactic acid concentration and oxygen consumption during exercise. No side effects of the therapy were reported.
Webster (1998)	Trained cyclists	6	Assessment of the effects of the therapy on parameters of cycling performance	Randomised, double-blind, placebo-controlled, crossover	1.8 g (+ 1 g/day allithiamin)	Mixed supplement containing 55% pantothenic acid and 45% pantothenic acid	7 days (twice) prior to exercise assessment, separated by a 21-day washout period	No significant outcome differences associated with active-treatment or placebo. No side effects of the therapy were reported.
Haslam <i>et al.</i> (1984)	Children with attention deficit disorders	41	Assessment of the effectiveness of megavitamin therapy in improving behaviour	2-stage design; Stage 1: 3-month open trial Stage 2: 4 x 6-week, double-blind, placebo-controlled, repeated crossover periods (in subjects who showed significant behaviour improvement in	Weeks 1-2: 0 g Weeks 3-4: 0.4 g Weeks 5-6: 0.6 g Weeks 7-8: 0.8 g Weeks 9-10: 1.0 g Weeks 11-14: 1.2 g (+ doses of niacinamide, ascorbic acid and pyridoxine increasing to a	Calcium pantothenate	12 weeks +	Significant behavioural improvement in 29% of subjects during Stage 1, but no significant differences between drug and placebo behavioural ratings in Stage 2. Some patients experienced nausea and vomiting during the treatment:- 3 subjects did not complete stage 1, due to excessive vomiting, abdominal discomfort or an inability to swallow the vitamin capsules; Vitamin supplementation was associated with significantly raised serum transaminase levels, which was attributed by the authors

				Stage 1)	maximum of 3.0, 3.0 and 0.6 g, respectively)			as probably due to the niacinamide component of the therapy.
Vas <i>et al.</i> (1989)	Elderly, in-patient volunteers	21	Assessment of the effects of supplementation on the kinetics of sulphadimidine acetylation	Open	1.1 g	Pantothenol	7 days	No significant effect of supplementation on sulphamidine kinetics. No side effects of the therapy were reported.
Nice <i>et al.</i> (1984)	Trained male distance runners	18	Assessment of the effect of supplementation on exercise (running) performance	Double-blind, placebo-controlled	1 g	Pantothenic acid	2 weeks	No significant differences between active-treatment and placebo groups in parameters of running performance. No significant changes (other than those accounted for by haemoconcentration) in total protein, albumin, calcium, cholesterol, BUN, uric acid, creatinine, bilirubin, alkaline phosphatase, SGOT, Na ⁺ , K ⁺ , Cl ⁻ or HCO ₃ ⁻ . No side effects of the therapy were reported.
Eisenstein & Scheiner (1997) [not peer-reviewed]	Patients with osteo- (<i>n</i> = 21) or rheumatoid (<i>n</i> = 9) arthritis	30	Assessment of the effectiveness of supplementation in alleviating patient-reported symptoms of arthritis	Single-blind, placebo-controlled, crossover	1.0 g	Calcium pantothenate	2 x 14 days	Significant (<i>P</i> = 0.009) improvement in the rheumatoid arthritis group in comparison to pre-treatment but not placebo-treatment values; no beneficial effects observed in the osteoarthritis group. No side effects of the therapy were reported.
Cochrane & Leslie (1952)	patients with Lupus Erythematosus	37	Treatment of the effects of lupus erythematosus	Open	≤ 600 mg (mostly 0.4 g)	Calcium pantothenate	≤ 24 weeks	Individual disease cases either unchanged or worse. No side effects of the therapy were reported.
Moiseenok <i>et al.</i> (2000) [abstract]	Patients with viral hepatitis A, also receiving "standard basic therapy for the	156	Assessment of the effectiveness of the supplementation to improve immunological response	Participants were allocated to supplementation and control (no supplementation) groups (matched for	300-600 mg (calcium pantothenate) or 90-180 mg (pantethine)	Calcium pantothenate or pantethine	3-4 weeks	Improved immune response associated with calcium pantothenate and pantethine supplementation. No side effects of the therapy were reported.

	infection”			clinical state)				
Arnold <i>et al.</i> (1978)	Children with minimal brain dysfunction	31	Alleviation of the symptoms of minimal brain dysfunction	Randomised, double-blind, placebo-controlled	400 mg (+ 2 g niacin, 2 g ascorbic acid, 1 g glutamic acid and 200 mg pyridoxine hydrochloride)	Calcium pantothenate	2 weeks	No significant differences between placebo and active-treatment groups. No side effects of the therapy were reported.
Goldman (1948)	Patients with lupus erythematosus	14	Treatment of the symptoms of lupus erythematosus	Open study	200-400 mg	Calcium pantothenate	Not stated	The authors reported that treatment was associated with improvement of the inflammatory phase of the disease, and that there were no reactions to the therapy
Brenner (1982)	Children with hyperkinesia and cerebral dysfunction	100	Treatment of behavioural problems	Not randomised or blinded; periods of active and placebo treatment (progression to the next stage only in those subjects showing a positive response to active treatment). Stage 1 (100 subjects): 3 days placebo, followed by 3 days active treatment Stage 2 (15 subjects): 1 week active treatment, followed by 1 week placebo	218 mg	Calcium pantothenate	3 days	Subjects showed variously an improvement, deterioration or no change in behavioural symptoms. No side effects of the therapy were reported.
Vaxman <i>et al.</i> (1996)	Patients undergoing resection	27	Assessment of the effects of supplementation on	“randomised” (patients were assigned to either	Group 1 (<i>n</i> = 17): 200 mg (+ 1 g ascorbic acid)	Pantothenic acid	21 days	In skin (day 8): significantly increased Mg and Mn in group 2 as compared with group 1.

	surgery for tattoos		the improvement of skin trace element levels and wound healing	group according to their order of arrival in the ward)	Group 2 ($n = 10$): 900 mg (+ 3 g ascorbic acid)				In scars (day 21): significantly increased Mg, Mn and Cu, decreased iron in group 2 as compared with group 1. No direct differences between the groups in effectiveness of wound healing. No side effects of the therapy were reported.
Vaxman <i>et al.</i> (1995)	Patients undergoing resection surgery for tattoos	49	Assessment of the effects of supplementation on the improvement of skin wound healing	Randomised, double-blind, placebo-controlled	200 mg (+ 1.0 g ascorbic acid)	Pantothenic acid	21 days		In skin (day 8): significantly increased Fe levels and decreased Mn levels associated with active treatment. In scars (day 21): significantly decreased Mn, and increased Mg levels associated with active treatment. No significant differences in blood (non-supplement) vitamin levels between the groups at day 21, except thiamine concentrations, which were significantly higher in the active treatment group. No direct effect of supplementation on the effectiveness of wound healing. No side effects of the therapy were reported.
Haslock & Wright (1971)	Patients with osteoarthritis of the knee	41	Assessment of the effects of supplementation on alleviating the symptoms of arthrosis	Randomised, placebo-controlled	200 mg (+ 120 mg L-cysteine hydrochloride)	Calcium D-pantothenate	12 weeks		No significant difference observed between the effects of the active treatment and the placebo. 4 patients in the active-treatment group withdrew because of side-effects of headache, sleepiness, depression, memory loss, flatulence, and abdominal pain. [one patient in the placebo group did not complete the trial – reasons not stated]
Annand (1962)	Patients with “worn joint” osteoarthritis	26	Assessment of the effects of supplementation in alleviating the symptoms of arthrosis	Open	12.5 mg	Pantothenic acid	“cases treated over a period of 18 months		Reduction in severity of symptoms reported by 77% of patients. 3 subjects reported the gradual development of general asthenia and “leg-weariness”, recovering upon substitution of 12.5 mg/day pyridoxin for the pantothenic acid supplement:- the authors suggested that “a vitamin imbalance may have been at fault in these cases”.

Table 2. Acute toxicity of D-calcium pantothenate in mice and rats (Unna & Greslin, 1940, 1941)

	LD ₅₀ (g/kg bw)			
	Oral	Subcutaneous	Intraperitoneal	Intravenous
Mice	10.0	2.7	0.92	0.91
Rats	> 10.0	3.4	0.82	0.83

ANNEX 2 TO EVM/01/01

INTAKES OF PANTOTHENIC ACID FROM FOOD AND SUPPLEMENTS

The data presented on pantothenic acid intakes are obtained from dietary surveys of specific population age groups in Britain carried out over the last 15 years²³⁴⁵⁶. In each survey food consumption data were collected by means of a dietary record (usually weighed) kept for 4 or 7 consecutive days. Nutrient intakes were calculated using a set of nutrient composition data contemporaneous with the time of the survey. Therefore some apparent differences in intakes between population age groups may be due to changes in the nutrient composition data and reflect changes in the nutrient composition of manufactured foods over time.

Total intakes of pantothenic acid

Table 1 provides information on the absolute intakes of pantothenic acid by the British population, from food sources and from all sources (including dietary supplements) classified by age and sex. Mean and median intake, and the upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), are given.

Average intakes of pantothenic acid were lowest for young children aged 1½ to 4½ years and highest for males aged 16-64 years. Mean pantothenic acid intakes increased markedly with age for boys aged 4-18 years, and decreased significantly with age for older people free-living in the community. Dietary supplements made a significant contribution to average intakes for adult females and older females living in the community.

There are no Dietary Reference values set for pantothenic acid. However mean pantothenic acid intake for infants exceeded the safe intake of 1.7 mg/d set for this age group, and mean intakes for adults and older people were within the range considered to be safe and adequate (3-7mg/d).

Intakes at the 97.5%ile were about 1.5 to 2 times the median in all the groups and exceeded the upper level for safe and adequate intakes (7mg) for almost all age groups from 4-6 years upwards.

Table 2 provides information on pantothenic acid intakes from food and supplements adjusted for body weight and classified by age and sex. Body weight adjusted pantothenic acid intakes are highest in infants and show a trend to decrease with age for children and young people.

² Food and nutrient intakes of British infants. 1986

³ National Diet and Nutrition Survey of children aged 1½-4½ years. 1992/3

⁴ National Diet and Nutrition Survey of young people aged 4-18 years. 1997/8

⁵ Dietary and nutritional survey of British adults. 1986/7

⁶ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

Sources of pantothenic acid in the diet

Table 3 indicates the contribution made by different types of food to average intakes of pantothenic acid by young people aged 15-18 years. This dataset was collected in 1997 and so most closely reflects current eating habits and fortification practices.

The main food sources of pantothenic acid in this age group were milk and milk products, cereals and cereal products and meat and meat products. Milk and milk products provided 24% of average intake, the majority of which came from milk. Cereals and cereal products provided 23%, of which breakfast cereals provided 9% and bread 6%. Some breakfast cereals are fortified with pantothenic acid, to a level of around 5-6 mg per 100 g of product. Meat and meat products provided 22%. Vegetables, potatoes and savoury snacks provided 18% of pantothenic acid intake, of which half came from potatoes.

The main sources were similar in other age groups except that the contribution from milk tended to be higher in young children. Infants obtained most of their pantothenic acid intake from milk and milk products, a quarter from infant formulas and a quarter from cows milk. Commercial infant foods provided about a fifth of intake.

Pantothenic acid intakes from supplements

Dietary supplements provided very little pantothenic acid for children or young people and their contribution to average intakes was negligible.

In adults, supplements provided 12% of mean intake of pantothenic acid for females and 5% for males. For older people free-living in the community, dietary supplements provided 2% of average intakes of pantothenic acid for males and 10% for females. For older people living in institutions the contribution from supplements was much smaller, 1% of average intakes.

Of course, the proportion of intake from supplements is much higher if supplement consumers are considered separately.

Table 4 shows the number of consumers of dietary supplements containing pantothenic acid in each age group, together with the mean, median and range of intakes from supplements for those who consumed them. No more than 4% of any group studied used supplements containing pantothenic acid. The range of intakes from supplements was wide and maximum intakes for adults and older females were well above the range set for safe and adequate intake.

Diet and Nutrition Surveys Branch
Nutrition Division
Food Standards Agency
January 2001

Table 1: Total intakes of Pantothenic acid

Age/sex	Absolute Pantothenic acid intake (mg/day) ⁷							
	Food Only				Food and Supplements			
	2.5% ile	Mean	Median	97.5%ile	2.5% ile	Mean	Median	97.5%ile
Infants (1986) 6-12mths/M&F	1.9	3.7	3.4	7.0	*	*	*	*
Pre-school children								
1½-2½ yrs/M/F	1.2	2.7	2.6	4.8	1.2	2.7	2.6	5.3
2½-3½ yrs/M/F	1.4	2.7	2.6	4.8	1.4	2.7	2.6	5.3
3½-4½ yrs/M	1.4	2.8	2.7	4.6	1.4	2.9	2.7	4.9
3½-4½ yrs/F	1.4	2.7	2.6	4.5	1.4	2.7	2.6	4.8
Young people (1997/8)								
4-6 yrs/M	2.1	4.4	4.2	7.5	2.1	4.4	4.2	8.0
4-6 yrs/F	2.1	4.0	3.9	6.9	2.1	4.1	3.9	7.4
7-10 yrs/M	2.8	4.7	4.6	7.6	2.8	4.8	4.6	7.7
7-10 yrs/F	2.3	4.1	4.0	6.7	2.3	4.2	4.0	7.0
11-14 yrs/M	2.1	5.2	4.9	9.2	2.1	5.2	4.9	9.2
11-14 yrs/F	1.8	4.2	4.0	7.6	1.8	4.2	4.0	7.6
15-18 yrs/M	2.7	5.8	5.4	10.8	2.7	5.8	5.5	10.8
15-18 yrs/F	1.6	4.0	4.0	7.7	1.6	4.1	4.0	8.9
Adults (1986/7)								
16-24 yrs/M	2.7	6.3	6.0	11.7	2.7	6.5	6.1	14.8
16-24 yrs/F	2.1	4.4	4.3	7.4	2.1	4.4	4.3	7.5
25-34 yrs/M	3.3	6.4	6.1	10.5	3.3	6.9	6.1	11.2
25-34 yrs/F	2.0	4.5	4.5	7.5	2.0	4.7	4.6	8.5
35-49 yrs/M	2.9	6.4	6.2	10.4	2.9	6.6	6.2	10.7
35-49 yrs/F	2.5	4.7	4.5	8.2	2.5	5.3	4.6	9.1
50-64 yrs/M	3.2	6.1	5.8	10.2	3.2	6.3	5.8	10.6
50-64 yrs/F	2.1	4.4	4.3	7.0	2.1	5.6	4.4	11.1
Older people free-living in the community (1994/5)								
65-74yrs/M	2.4	5.2	5.2	8.1	2.4	5.3	5.2	9.6
65-74yrs/F**	2.1	4.1	4.0	6.7	2.2	4.7(5.1)	4.1	7.3
75-84 yrs/M	2.4	4.7	4.4	8.0	2.4	4.7	4.4	8.2
75-84 yrs/F	1.8	3.8	3.5	6.6	1.8	4.0	3.5	7.6
85 and over/M	2.0	4.3	4.1	6.7	2.0	4.4	4.1	9.0
85 and over/F	1.5	3.5	3.4	6.2	1.5	3.6	3.5	7.5
Older people living in institutions (1994/5)								
65-84 yrs/M	2.2	4.5	4.4	7.2	2.2	4.5	4.4	7.2
65-84 yrs/F	2.5	4.1	4.0	6.7	2.4	4.1	4.0	6.7
85 and over/M	2.3	4.5	4.6	7.1	2.3	4.5	4.6	7.1
85 and over/F	2.1	3.7	3.5	6.2	2.1	3.8	3.5	6.2

* Data unavailable

** The pantothenic acid intake values including supplements for 2 women in the 65-74 year age group were very high and were trimmed. The values trimmed were 94.8 and 55.0mg/day. Intake for the group before trimming is given in brackets.

Table 2: Bodyweight adjusted Pantothenic acid intake

Age/sex	Bodyweight adjusted Pantothenic acid intake (mg/kg bwt /day) ⁸		
	<i>intakes from food and supplements</i>		
	Mean	Median	97.5%ile
Infants (1986)⁹ 6-12mths/M&F	0.40	0.36	0.78
Pre-school children (1992/3) 1½-2½ yrs/M&F	0.22	0.21	0.45
2½-3½ yrs/M&F	0.19	0.18	0.35
3½-4½ yrs/M	0.17	0.17	0.32
3½-4½ yrs/F	0.17	0.16	0.30
Young people (1997/8) 4-6 yrs/M	0.21	0.20	0.40
4-6 yrs/F	0.20	0.19	0.35
7-10 yrs/M	0.16	0.15	0.26
7-10 yrs/F	0.14	0.13	0.24
11-14 yrs/M	0.11	0.11	0.20
11-14 yrs/F	0.09	0.08	0.17
15-18 yrs/M	0.09	0.09	0.16
15-18 yrs/F	0.07	0.07	0.13
Adults (1986/7) 16-24 yrs/M	0.09	0.09	0.21
16-24 yrs/F	0.07	0.07	0.13
25-34 yrs/M	0.09	0.08	0.15
25-34 yrs/F	0.08	0.07	0.14
35-49 yrs/M	0.09	0.08	0.15
35-49 yrs/F	0.08	0.07	0.15
50-64 yrs/M	0.08	0.08	0.14
50-64 yrs/F	0.09	0.07	0.17
Older people free-living in the community (1994/5) 65-74 yrs/M	0.07	0.07	0.12
65-74 yrs/F	0.08	0.06	0.13
75-84 yrs/M	0.07	0.06	0.12
75-84 yrs/F	0.06	0.06	0.13
85 and over/M	0.07	0.06	0.12
85 and over/F	0.06	0.06	0.15
Older people living in institutions (1994/5) 65-84 yrs/M	0.07	0.06	0.12
65-84 yrs/F	0.07	0.07	0.11
85 and over/M	0.07	0.07	0.11
85 and over/F	0.07	0.06	0.12

⁸ Body weights measured for each subject for all age groups except infants aged 6-12 months where reported body weights were used.

⁹ Intakes for infants aged 6-12 months are from food only.

Table 3¹⁰: Sources of Pantothenic acid in the diet

Food Type	Contribution of food types to average daily intake of pantothenic acid	
	mg/day	% of total
Cereal and cereal products	1.13	23
- of which breakfast cereals	0.43	9
- of which bread	0.32	6
Milk and milk products	1.19	24
- of which milk	1.04	21
Egg and egg dishes	0.14	3
Fat spreads	0.00	0
Meat and meat products	1.07	22
of which chicken and turkey dishes	0.29	6
Fish and fish dishes	0.07	1
Vegetables, potatoes and savoury snacks	0.90	18
- of which roast/fried potatoes and chips	0.27	5
- of which boiled, mashed, baked potatoes	0.19	4
Fruits and nuts	0.09	2
Sugar, confectionery and preserves	0.13	3
Beverages	0.15	3
Miscellaneous	0.07	1
Total intake from food	4.96*	100
<i>Intake from dietary supplements</i>	<i>0.05</i>	<i>1</i>
Total intake from food and supplements	5.01	100

* Allows for rounding

¹⁰ NDNS: young people aged 4-18 years. 1997/8. 15-18 year group

Table 4: Pantothenic acid intake from supplements

<i>Age/sex</i>	Consumers of Pantothenic acid supplements		Pantothenic acid intake from supplements (consumers only) (mg/day)		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<i>Infants (1986)</i> 6-12 mths/M&F	*	*	*	*	*
<i>Pre-school children (1992/3)</i> 1½-4½ yrs/M&F	34	2	2.6	2.9	0.4-5.0
<i>Young people (1997/8)</i> 4-6 yrs/M&F	6	2	3.4	3.6	0.9-6.0
7-10 yrs/M&F	8	2	1.5	1.1	0.5-3.2
11-14 yrs/M	1	<1	0.7	0.7	0.7
11-14 yrs/F	1	<1	2.3	2.3	2.3
15-18 yrs/M	2	1	0.7	0.7	0.7
15-18 yrs/F	4	2	4.4	4.8	2.5-6.0
<i>Adults (1986/7)</i> 16-64 yrs/M	24	2	12.4	4.3	0.1-107.1
16-64 yrs/F	46	4	12.8	4.3	0.3-188.6
<i>Older people free-living in the community (1994/5)</i> 65 and over/M	19	3	3.3	4.0	0.1-6.0
65 and over/F	22	3	17.5	4.2	0.0-90.0
<i>Older people living in institutions (1994/5)</i> 65 and over/M	2	1	1.2	0.3	0.3-2.2
65 and over/F	5	2	2.0	0.5	0.4-13.2

* Data unavailable

ANNEX 3 TO EVM/01/01

Pantothenic Acid : Summary table of selected nutrition related information and existing guidance on regulations

Unit of usage	mg/day		Mg/100 kcal
	Male	Female	
<i>UK Safe Intake</i>			
Adults	3-7		
Infants	1.7		
<i>Mean adult UK dietary intake from food (all sources)</i>			
Adults (16-64) ¹¹	6.3 (6.6)	4.5 (5.1)	
65 years and over ¹²			
free living	5.0 (5.1)	3.9 (4.4)	
institutionalised	4.5 (4.5)	3.9 (3.9)	
EU labelling RDA ¹³	6		
Supplemental doses	50-550		
Regulations			
Infant formula ¹⁴			minimum 300µg/100kcal
Infant foods ¹⁵			1.5
Weight reduction ¹⁶			
whole daily diet replacement	3 per day		
meal replacement	0.9 per meal		
<i>Maximum total safe daily intake</i> ¹	10 g+		
EHPM 1997 ¹⁷	1000		

¹¹ Dietary and nutritional survey of British adults. 1990

¹² National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹³ The Food Labelling Regulations 1996

¹⁴ The Infant Formula and Follow-on Formula Regulations 1995

¹⁵ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1999 (amended)

¹⁶ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

¹⁷ Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.