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Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Pantothenic Acid

(expressed on 17 April 2002)

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FOREWORD

This opinion is one in the series of opinions of the Scientific Committee on Food (SCF) on the upper levels of vitamins and minerals. The terms of reference given by the European Commission for this task, the related background and the guidelines used by the Committee to develop tolerable upper intake levels for vitamins and minerals used in this opinion, which were expressed by the SCF on 19 October 2000, are available on the Internet at the pages of the SCF, at the address: http://www.europa.eu.int/comm/food/fs/sc/scf/index_en.html.

1. INTRODUCTION

Pantothenic acid, sometimes designated as vitamin B_5 (in some text books also as B_3), is N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine. D-Pantothenic acid (MW 219.23) is the only occurring natural form. Free pantothenic acid and its sodium salt are chemically unstable, and therefore the usual pharmacological preparation is the calcium salt (calcium pantothenate). The alcohol, panthenol, is a synthetic form which can be oxidised *in vivo* to pantothenic acid. It is included in the list of substances that may be used in the manufacture of foods for particular nutritional uses and in food supplements (the legal measure on food supplements is expected to be adopted in the immediate future). Panthenol is widely used in cosmetic products.

Calcium pantothenate, commercially available as the D-isomer or D,L-racemate, is stable in neutral solution, and destroyed by heat, and at alkaline or acid pH. In most dietary sources, and in biological tissues, pantothenic acid is present as coenzyme A and 4'-phosphopantetheine.

2. NUTRITIONAL BACKGROUND AND METABOLISM

Pantothenic acid was first shown to be an essential factor in 1933 for the growth of yeast and in curing of (deficiency-induced) dermatitis in chickens. Pantothenic acid plays a central role in intermediary metabolism as part of the coenzyme A (CoA) molecule and as part of the pantotheine functional group in the acyl-carrier protein (Acyl-CP). This vitamin serves therefore as a cofactor in acyl-group activation and transfer in fatty acid and carbohydrate metabolism, as well as in a wide range of (other) acylation reactions (see Fox, 1984 and Plesofsky-Vig, 1996 for reviews). The synthesis of CoA is regulated by pantothenate kinase, which is under control of the end products (CoA and acyl-CP).

Pantothenic acid is widely distributed among foods, especially high concentrations are found in yeast and organ meat (liver, kidney), but eggs, milk, whole grain cereals and vegetables (e.g. broccoli) are good sources. In most foods it is present in bound form (as CoA), requiring enzymatic treatment for analysis of total contents. Ingested pantothenic acid is first hydrolysed to pantotheine and subsequently to free pantothenic acid by pantotheinase in the

intestinal lumen. Although in earlier studies simple diffusion was reported to be the main transport system, there is now ample evidence that transport is effected in mammals through a saturable, sodium dependent transport system in the jejunum (Fenstermacher and Rose, 1986; Stein and Diamonds, 1989). The intestinal flora can produce pantothenic acid and animals practising coprophagy such as, rats and mice, can use faeces as a "dietary" source. It is not yet clear whether there is also direct uptake in the colon.

Data on bioavailability of pantothenic acid from foods in humans is limited. In one study (Tarr *et al.*, 1981) availability of pantothenate from an average American diet was assessed by comparing urinary excretion levels after controlled feeding (during 5 weeks) of an average American diet, containing 11.5 mg pantothenate, and a formula diet supplemented with 6.0 mg pantothenate (total intake 8.2 mg), respectively. An average "relative" bioavailability of 50% (range: 40-61%; n=6) was calculated, assuming 100% availability from the synthetic form. About 60% of an oral dose of 10 and 100 mg/day, respectively, was excreted as intact pantothenic acid (Fry *et al.*, 1976). Urinary excretion (normal range between 2-7 mg [9-32 μmol]/day) reflects dietary intake, although a wide range of individual variation has been noted.

In blood, pantothenic acid occurs both in plasma and in red blood cells. Whole blood concentrations are reported to be ca. 2 μmol/L, and is considered to reflect status, although there are only few data available to substantiate this conclusion.

Deficiency in humans is rare because of the widespread availability of pantothenic acid in the usual diet. In underfed World War II prisoners of war in the Philippines painful burning sensations in their feet ("burning feet syndrome") and numb toes have been ascribed to a pantothenic acid deficiency. Symptoms reported from an experimentally induced deficiency in humans using the antagonist ω-methylpantothenate in combination with a pantothenic acid deficient diet, include non specific symptoms such as headache, fatigue, insomnia and paresthesia of hands and feet. Increased insulin sensitivity and a decreased eosinopenic response to ACTH, and loss of antibody production, have also been reported (see Plesofsky-Vig, 1996). In animals diet-induced deficiency symptoms are hypertrophy of the adrenal cortex and increased resistance to viral infections in rats; hypoglycaemia, gastrointestinal symptoms and convulsions in dogs, and dermatitis and poor feathering in chickens.

There are only limited data on the pantothenate requirements and the SCF could not establish a recommended intake. Average intakes in adults are about 4-7 mg/day, with a range of 3-12 mg/day. Such intakes were considered adequate to prevent deficiency, including during pregnancy and lactation (SCF, 1993). Mean (97.5 percentile) intake from food in Great Britain (UK 1986/87 survey; Gregory *et al.*, 1990) were 6.3 (10.5) and 4.5 (7.7) mg/day for men and women, respectively; and 6.6 (11.2) and 5.1 (9.1) mg/day, respectively, from all sources (food and supplements). For Ireland mean intakes from all sources (food and supplements) were reported as 6.5 (12.5) mg in men and 5.3 (14.4) mg in women, and from food sources only as 6.1 (10.4) and 4.3 (7.2) mg/day, respectively (IUNA, 2001).

Recently the Institute of Medicine Committee (IOM, 1998) estimated the level of adequate intake (AI) for pantothenic acid at 5 mg/day for adults, based upon replacement of the amount lost by urinary excretion.

3. HAZARD IDENTIFICATION

In the studies on pantothenic acid which were reviewed it was not specified whether D or D,L forms were used and therefore the conclusions drawn relate to both isomers.

3.1 Data from studies in animals

For mice and rats, a subcutaneous LD_{50} has been reported for pantothenic acid of 2.7 g/kg bw and 3.4 g/kg bw, respectively; the oral LD_{50} for mice was 10 g/kg bw, death due to respiratory failure (Unna and Greslin, 1941). Following repeated oral dosing in rats (50-200 mg/day for 190 days), in dogs (50 mg/kg bw/day for 6 months), and in monkeys (1 g/day; 250-400 mg/kg bw/day for 6 months) no toxic effects were reported (Unna and Greslin, 1941).

According to the "Cosmetic ingredient review" (1987) on panthenol and pantothenic acid no teratogenic or foetotoxic effects are known for rats fed calcium pantothenate before mating and throughout gestation. No abnormal chemical, histochemical and histological abnormalities were observed in the liver, adrenal, duodenum and tibia of the young rats at birth, born from females receiving 100 μg or 1 mg calcium pantothenate daily during pregnancy (Everson *et al*., 1954; Chung *et al*., 1954). In the offspring of the group of rats treated with 50 mg/day, which were fed with the same daily dose as soon as they were weaned, a normal development was observed and weight gain comparable to the control group (Unna and Greslin, 1941).

No toxicological effects have been reported for D- and D,L-panthenol in subchronic oral toxicity studies in rats with dosages between 20-200 mg/day for 90 days; and with 2 mg/day for 6 months (studies cited in the "Cosmetic ingredient review", 1987)

3.2 Data from studies in humans

No data have been reported on pantothenic acid or panthenol toxicity in humans. A Medline and Toxline search from 1966 on did not reveal any report on adverse effects after oral intake of pantothenic acid or panthenol.

High dosages were used in a placebo-controlled, double-blind trial on the potential beneficial effect of pantothenic acid in treatment of patients with arthritic symptoms (General Practitioner Research Group, 1980). In this study 94 patients were treated for 8 weeks with dosages of calcium pantothenate, starting with 500 mg/day in the first two days, then 1 g/day for the next three days, 1.5 g/day the following four days, and 2 g/day from day 10 until the end of the trial (47 patients treated; 46 on placebo). In this study no side effects of treatment were noted, while some evidence was obtained for a beneficial effect on pain and disability in the subgroup of rheumatoid arthritis patients. Other therapeutic trials, such as in wound healing, using dosages between 0.2-0.9 g/day also reported no adverse (nor beneficial) effects (Vaxman, 1996).

In one study in children with attention deficit disorders (n=41) treated with 1.2 g pantothenic acid per day, in combination with 3 g nicotinamide, 3 g ascorbic acid and 0.6 g pyridoxine, increased serum transaminase levels were reported for 17 children, treated for 12 weeks (Haslam *et al.*, 1984). Whether this hepatotoxic effect was related to the high dose of pantothenic acid, or to the combination with the high doses of nicotinamide, vitamin C and pyridoxine, cannot be concluded from this study, and therefore, this study cannot be used in risk assessment of pantothenic acid. Occasional diarrhoea and water retention might occur at

daily dose levels of 10-20 g/day, as found in studies on stress protection and prevention of greying of hair (studies mentioned in a review by Fox, 1984, and in a Cosmetic Ingredient review on the safety of panthenol and pantothenic acid, 1987).

4. DOSE RESPONSE AND DERIVATION OF TOLERABLE UPPER INTAKE LEVEL (UL)

Owing to the lack of systematic oral dose response intake studies and the very low toxicity of pantothenic acid (calcium pantothenate or panthenol) no LOAEL and NOAEL can be established and no numerical UL can be derived.

5. CHARACTERIZATION OF RISK

Pantothenic acid apparently has a very low toxicity and minor adverse gastrointestinal effects such as occasional diarrhoea and water retention occurred only at very high intake levels (10-20 g/day). Average intakes in adults range between 3-12 mg/day, and this intake level is considered as adequate. Few data on distribution of intakes from dietary and supplement sources are available. In Ireland the 97.5 percentile of intakes from all sources (food and supplements) was reported 12.5 mg in men and 14.4 mg in women, and from food sources only as 10.4 mg and 7.2 mg per day, respectively (IUNA, 2001). For the UK the 97.5 percentile of intakes reported for all sources (food and supplements) was 11.2 mg in men and 9.1 mg in women, and from food sources only as 10.5 mg and 7.7 mg per day, respectively (Gregory *et al.*, 1990).

Although it is not possible to derive a numerical UL for pantothenic acid evidence available from clinical studies using high doses of pantothenic acid indicates that intakes considerably in excess of current levels of intake from all sources do not represent a health risk for the general population.

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