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DRAFT SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for pantothenic acid[1]

EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for pantothenic acid. Pantothenic acid is a water-soluble vitamin, which is a component of coenzyme A (CoA) and acyl-carrier proteins. Pantothenic acid is ubiquitous and deficiency is rare. There are no suitable biomarkers that can be used for deriving the requirement for pantothenic acid. Data available on pantothenic acid intakes and health consequences are very limited and cannot be used for deriving DRVs for pantothenic acid. As there is insufficient evidence available to derive an Average Requirement and a Population Reference Intake, an Adequate Intake (AI) is proposed. The setting of AIs is based on observed pantothenic acid intakes with a mixed diet and the apparent absence of signs of deficiency in the EU, suggesting that current intake levels are adequate. The AI for adults is set at 5 mg/day. The AI for adults also applies to pregnant women. For lactating women, an AI of 7 mg/day is proposed, to compensate for pantothenic acid losses through breast milk. For infants over six months, an AI of 3 mg/day is proposed by extrapolating from the pantothenic acid intake of exclusively breast-fed infants aged zero to six months, using allometric scaling based on reference body weights of the respective age groups, in order to account for the role of pantothenic acid in energy metabolism. The AI for children and adolescents is set at 4 and 5 mg/day, respectively, based on observed intakes in the EU.

KEY WORDS

pantothenic acid, Dietary Reference Value, Adequate Intake

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on Dietary Reference Values (DRVs) for the European population, including pantothenic acid.

In 1993, the Scientific Committee for Food (SCF) proposed an Acceptable Range of Intakes of pantothenic acid for adults of 3–12 mg/day, based on observed intakes of pantothenic acid in European countries, which were considered adequate to meet requirements and prevent deficiency.

Pantothenic acid is a water-soluble vitamin, which is a component of coenzyme A (CoA) and acyl-carrier proteins. Pantothenic acid is ubiquitous and deficiency is rare. Foods rich in pantothenic acid include meat (products), eggs, nuts, avocados and cruciferous vegetables. Main contributors to pantothenic acid intakes include meat products, bread, milk-based products and vegetables.

Data on pantothenic acid absorption are lacking. Most of the pantothenic acid in tissues is present as CoA, mainly found in mitochondria, with lesser amounts present as acyl carrier protein and free pantothenic acid. Pantothenic acid is excreted in urine, after hydrolysis of CoA in a multistep reaction.

Urinary excretion of pantothenic acid and, to a lesser extent, pantothenic acid concentration in whole blood or erythrocytes reflect pantothenic acid intake. Data from the general population are limited so that the variability characteristics of these biomarkers and their ability to discriminate between pantothenic acid insufficiency and adequacy are not well known. No cut-off values have been established for these biomarkers. The Panel considers that there are no suitable biomarkers that can be used for deriving the requirement for pantothenic acid.

Data available on pantothenic acid intakes and health consequences are very limited and cannot be used for deriving DRVs for pantothenic acid.

As the evidence to derive an Average Requirement and thus a Population Reference Intake is considered insufficient, an Adequate Intake (AI) is proposed for all population groups. There is no indication that the AI should be different according to sex. The setting of AIs is based on observed pantothenic acid intakes with a mixed diet and the apparent absence of signs of deficiency in the EU, suggesting that current intake levels are adequate. Estimates of pantothenic acid intakes in children and adolescents, adults and older adults were available from eight EU countries. In boys and girls (3–12 years) in the EU, mean/median intakes of 3.0 to 5.7 mg/day were reported, while mean/median intakes of 3.0 to 7.2 mg/day were observed in adolescent boys and girls (11–19 years). In adult men and women below about 65 years, mean/median intakes of 3.2 to 6.3 mg/day were reported, while mean/median intakes were between 2.2 and 6.0 mg/day in older men and women. Data on pantothenic acid intakes in pregnancy were scarce.

The AI for adults is set at 5 mg/day. The AI for adults also applies to pregnant women. For lactating women, an AI of 7 mg/day is proposed, to compensate for pantothenic acid losses through breast milk. For infants over six months, an AI of 3 mg/day is proposed by extrapolating from the pantothenic acid intake of exclusively breast-fed infants aged zero to six months, using allometric scaling based on reference body weights of the respective age groups to the power of 0.75, in order to account for the role of pantothenic acid in energy metabolism, and rounding to the nearest unit. The AI for children and adolescents is set at 4 and 5 mg/day, respectively, based on observed intakes in the EU.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and if necessary to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an opinion on the nutrient and energy intakes for the European Community[4]. The report provided Reference Intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context the EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context the EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1)(a) and Article 31 of Regulation (EC) No 178/2002, the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance the EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically advice is requested on the following dietary components:

- Carbohydrates, including sugars;
- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;
- Protein;

[4] Scientific Committee for Food, Nutrient and energy intakes for the European Community, Reports of the Scientific Committee for Food 31st series, Office for Official Publication of the European Communities, Luxembourg, 1993.

- Dietary fibre.

Following on from the first part of the task, the EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, the EFSA is asked to provide guidance on the translation of nutrient based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

ASSESSMENT

1. Introduction

In 1993, the Scientific Committee for Food (SCF) adopted an opinion on the nutrient and energy intakes for the European Community but was unable to define a specific physiological requirement of pantothenic acid for human health (SCF, 1993). It was stated that average intakes in adults were about 4–7 mg/day, but that individuals consumed from 3 to 12 mg/day. The SCF proposed an Acceptable Range of Intakes of pantothenic acid for adults of 3–12 mg/day, which was considered adequate to meet requirements and prevent deficiency. The SCF considered that there was no information on which to base additional requirement for pantothenic acid in pregnancy or lactation. The SCF did not set reference values for infants and children.

2. Definition/category

2.1. Chemistry

Pantothenic acid (also called vitamin B5) is a water-soluble vitamin, which is synthesised by microorganisms via an amide linkage of β-alanine and D-pantoic acid (Trumbo, 2006). The only form found in nature that is biologically active is D-pantothenic acid. The molar mass of pantothenic acid is 219.23 Da. Pantothenic acid can be quantified in food and human tissues by well established methods (IOM, 1998; Mittermayer et al., 2004; Pakin et al., 2004; Trumbo, 2006; Andrieux et al., 2012).

2.2. Function, physiology and metabolism

Pantothenic acid is a component of coenzyme A (CoA) and acyl-carrier proteins and serves in acyl-group activation and transfer, which is essential for fatty acid synthesis and oxidative degradation of fatty acids and amino acids. Humans cannot synthetise pantothenic acid and depend on its dietary intake.

Dietary CoA is hydrolysed in the intestine to dephospho-CoA, phosphopantetheine, and pantetheine. The latter is further hydrolysed to pantothenic acid (Trumbo, 2006). Intestinal absorption of pantothenic acid occurs via a saturable sodium-dependent carrier-mediated process, which predominates over passive diffusion at physiological concentrations (Stein and Diamond, 1989; Prasad et al., 1999). There are few quantitative data on pantothenic acid absorption. A mean absorption efficiency of 50 % (range: 40–61 %) of dietary pantothenic acid was estimated based on urinary pantothenic acid excretion of six healthy young men (Tarr et al., 1981). Although intestinal microbiota produce pantothenic acid, the extent to which it is absorbed from the large intestine and contributes to pantothenic acid requirements is uncertain (Trumbo, 2006).

In blood, pantothenic acid is transported mainly as CoA within erythrocytes (Trumbo, 2006). Pantothenic acid uptake in tissues occurs through an active sodium-dependent mechanism. Most of the pantothenic acid in tissues is present as CoA, mainly found in mitochondria, with lesser amounts present as acyl-carrier protein and free pantothenic acid. Pantothenic acid is excreted in urine, after hydrolysis of CoA in a multistep reaction. In a few groups of healthy subjects, average daily urinary excretion of pantothenic acid was observed to range between about 2.0 and 3.5 mg/day in children and adolescents (Schmidt, 1951; Kathman and Kies, 1984; Eissenstat et al., 1986) and between about 2.0 mg and 4.0 mg/day in adults (Schmidt, 1951; Fox and Linkswiler, 1961; Fry et al., 1976; Kathman and Kies, 1984; Song et al., 1985). Urinary excretion of pantothenic acid is positively correlated to pantothenic acid intakes (Section 2.3).

Placental transport of pantothenic acid has been suggested to involve an active mechanism (Grassl, 1992; Wang et al., 1999).

The concentration of pantothenic acid in mature human milk has been shown to correlate with maternal intake and urinary excretion of the vitamin (Song et al., 1984). Mean concentrations of pantothenic acid in mature human milk typically range between 2 and 3 mg/L (data from the UK, US and Japan, up to one year of lactation) (DHSS, 1977; Ford et al., 1983; Song et al., 1984; Sakurai et al., 2005), although a mean concentration up to 6.7 mg/L has been found in a group of mothers in the US taking or not supplements (Johnston et al., 1981) (Appendix A).

Pantothenic acid is ubiquitous in foods and dietary deficiency is rare. Deficiency symptoms have been described in subjects on a pantothenic acid antagonist and/or pantothenic acid-deficient diet and include mood changes, as well as sleep, neurological, cardiac and gastrointestinal disturbances (Smith and Song, 1996; SCF, 2002; Trumbo, 2006).

The SCF noted that pantothenic acid has a low toxicity (SCF, 2002). A Tolerable Upper Intake Level (UL) for pantothenic acid could not be derived but evidence available from clinical studies using high doses of pantothenic acid (up to 2 g/day) indicates that intakes considerably in excess of observed levels of intake from all sources do not represent a health risk for the general population (SCF, 2002).

Although biotin and pantothenic acid have been shown to share common carrier-mediated uptake mechanisms *in vitro* (Said, 2009), nutritional implications of this interaction are not known.

2.3. Biomarkers

Positive linear correlations (r range: 0.3–0.6) between pantothenic acid intakes (range of means: 4.8–6.3 mg/day) and 24-hour urinary excretion have been reported in groups (n = 37 to 156, according to study) of male and female adolescents (Eissenstat et al., 1986), pregnant, lactating and non-pregnant-non-lactating women (Song et al., 1985), male and female schoolchildren (Tjusi et al., 2011), young men and women (Tjusi et al., 2010b), and elderly women (Tjusi et al., 2010a). No differences in urinary excretion were observed between sexes despite intakes being significantly higher in adolescent males compared to females (Eissenstat et al., 1986), whereas the influence of sex was not investigated in other mixed populations (Tjusi et al., 2011, Tjusi et al. 2010b).

In intervention trials with small groups of young women (n = 6–8), linear dose-response relationships have been described in subjects consuming a self-chosen diet (6.7 ± 2.1 mg/day) or given doses of 2.8, 7.8 and 12.8 mg/day pantothenic acid for ten-day periods (r = 0.8) (Fox and Linkswiler, 1961) and 9.3 mg, 14.1 mg, 24.3 mg and 40.7 mg for four-day periods (r = 0.95) (Fukuwatari and Shibata, 2008). In both studies, urinary excretion was observed to be lower (30-60 %) than intake at all doses tested, except at the lowest intake of 2.8 mg/day for which the mean urinary excretion was 3.2 mg/day. Upon depletion with a pantothenic acid-free diet for nine weeks, urinary excretion decreased to 0.79 ± 0.17 mg/day in six men compared to a urinary pantothenic acid excretion of 3.05 ± 1.2 mg/day at baseline at intakes of 6.45 mg/day (range: 4.85–8.16 mg/day) (Fry et al., 1976).

In the study in adolescents by Eissenstat et al. (1986), positive correlations were also reported between pantothenic acid intakes and its concentrations in erythrocytes (r = 0.65) or in whole blood (r = 0.38) (mean intake of about 5 mg/day from food only). No differences in pantothenic acid concentration in erythrocytes or whole blood were observed between sexes. Positive correlation between pantothenic acid intakes and its concentrations in whole blood has also been observed in non-institutionalised older adults (mean intake of about 11 mg/day from food and supplements) (r = 0.38), but not in institutionalised subjects (Srinivasan et al., 1981).

In a group of six men depleted in pantothenic acid for nine weeks, whole blood pantothenic acid concentration was found to be less sensitive to changes in intake than urinary concentration of pantothenic acid (Fry et al., 1976).

Plasma/serum concentrations of pantothenic acid were reported to not correlate with dietary intakes (Song et al., 1985; IOM, 1998).

The Panel notes that urinary pantothenic acid excretion reflects recent pantothenic acid intake and that moderate correlations have also been observed between pantothenic acid intakes and its concentrations in whole blood or erythrocytes. However, data from the general population are limited so that the variability characteristics of these biomarkers and their ability to discriminate between pantothenic acid insufficiency and adequacy are not well known. No cut-off values have been established for these biomarkers.

3. Dietary sources and intake data

3.1. Dietary sources

Pantothenic acid is present in a wide variety of foods. Foods rich in pantothenic acid include meat (products), eggs, nuts, avocados and cruciferous vegetables (FSA, 2002; Anses/CIQUAL, 2012). Main contributors to pantothenic acid intakes include meat products, bread, milk-based products and vegetables (Afssa, 2009; DGE, 2012).

Currently, pantothenic acid (as D-pantothenate, calcium; D-pantothenate, sodium or dexpanthenol) may be added to food supplements[5] and foods.[6] The pantothenic acid content of infant and follow-on formulae is regulated.[7]

3.2. Dietary intakes

Estimates of pantothenic acid intakes in children and adolescents, adults and older adults from eight EU countries (Austria, France, Germany, Hungary, Ireland, Poland, Portugal and Latvia, data collected between 1996 and 2010) are provided in Appendices B, C and D, respectively. Values were calculated from individual consumption data collected from dietary history, three-/four-/seven-day dietary records, 24-hour recall, or food frequency questionnaires, combined with analytical data from food composition tables. Dietary intake data are prone to reporting errors and there is a varying degree of under-reporting in different surveys (Merten et al., 2011). Although the differences in methodologies have an impact on the accuracy of between-country comparisons, the data presented give an overview of the pantothenic acid intake in a number of European countries.

Data in young children are limited to a survey in Irish young children (1–4 years) using four-day weighed dietary records, where a median pantothenic acid intake of 4.1 mg/day was observed (IUNA, online-a).

In boys and girls (3–12 years) in the EU, mean/median intakes of 3.0 to 5.7 mg/day were reported. Median intakes ranged from 3.9 to 4.6 mg/day in France (3–10 years), from 4.4 to 5.7 mg/day in Ireland (5–12 years) and from 4.0 to 4.3 mg/day in Germany (6–11 years), while mean intakes ranged from 3.0 to 4.0 mg/day in Austria (7–12 years).

[5] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, OJ L 183, 12.7.2002, p. 51.

[6] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, OJ L 404, 30.12.2006, p. 26.

[7] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p.1.

In adolescent boys and girls (11–19 years), mean/median intakes of 3.0 to 7.2 mg/day were reported. Median intakes ranged from 4.0 to 5.2 mg/day in France (11–17 years), from 4.2 to 6.6 mg/day in Ireland (13–17 years), from 5.5 to 7.2 mg/day (12–17 years, using the dietary history method) or from 3.1 to 4.0 mg/day (15–19 years, using 24-hour recalls) in Germany, while mean intakes ranged from 3.0 to 6.0 mg/day in Austria (13–19 years).

In adult men and women below about 65 years, mean/median intakes of 3.2 to 6.3 mg/day were reported. Data from France, Germany and Ireland indicated median intakes between 4.2 mg/day and 6.3 mg/day in men and 3.3 and 5.2 mg/day in women, while data in Austria, Hungary and Portugal indicated mean intakes of 4.0 to 5.4 mg/day in men and 3.2 to 4.7 mg/day in women.

In older men and women, mean/median intakes of 2.2 to 6.0 mg/day were reported. Data from France, Germany and Ireland indicated median intakes ranging from 4.2 to 6.0 mg/day in men and 3.6 to 5.2 mg/day in women, while data in Austria, Hungary, Poland and Portugal indicate mean intakes between 2.6 to 4.7 mg/day in men and 2.2 to 4.4 mg/day in women.

Data on pantothenic acid intakes in pregnancy are scarce. Some intake estimates are available from observational studies conducted in the US, the UK and Japan. In a population of Caucasian women in the US, Song et al. (1985) observed a mean (± SD) pantothenic acid intake of 5.3 (± 1.7) mg/day during the third trimester of pregnancy (n = 26) and 4.8 (± 1.6) mg/day in non-pregnant women (n = 17). In a study in Japanese women, Shibata et al. (2013) reported mean (± SD) pantothenic acid intakes of 5.7 (± 2.1) mg/day (second trimester, n = 24) and 5.7 (± 1.7) mg/day (third trimester, n = 32) in pregnant women and 5.0 (± 1.5) mg/day in non-pregnant women (n = 37). In a cohort of 42 pregnant women in the UK, mean (± SD) pantothenic acid intakes of 3.7 ± 1.2 mg/day, 3.9 ± 1.2 mg/day, 3.9 ± 1.0 mg/day, 3.6 ± 1.1 mg/day during the first, second, third trimesters of pregnancy and six weeks *post partum*, respectively, were observed, using four to seven days weighed dietary records (Derbyshire et al., 2009).

4. Overview of Dietary Reference Values and recommendations

Several national and international organisations and authorities have proposed reference values or recommendations for pantothenic acid intakes. There has been consensus so far that evidence is lacking to establish an Average Requirement (AR) for pantothenic acid. Rather, Adequate or Acceptable Ranges of Intakes have been proposed (Table 1). The Nordic countries did not set a reference value for pantothenic acid intake (NNR, 2012).

4.1. Adults

The SCF (1993) and the UK Committee on Medical Aspects of Food Policy (COMA) (DH, 1991)set Acceptable Ranges of Intakes and the US Institute of Medicine (IOM, 1998), the French Food Safety Agency (Afssa, 2001), the World Health Organization/Food and Agriculture Organization (WHO/FAO, 2004) and the German-speaking countries (D-A-CH, 2013) set Adequate Intakes (AIs), based on data from dietary intake surveys, considering the absence of deficiency at observed intakes. IOM also noted that the proposed AI was supported by the limited data available on the dose-response relationship between pantothenic acid intake and urinary excretion, which indicate that a pantothenic acid intake of approximately 4 mg/day would result in a similar amount of urinary excretion (Fox and Linkswiler, 1961).

4.2. Infants and children

The German-speaking countries (D-A-CH, 2013), WHO/FAO (2004) and Afssa (2001) proposed AIs for infants aged 7-12 months based on extrapolation from typical pantothenic acid intakes with human milk in younger exclusively breast-fed infants. Following the same approach, IOM (1998) estimated a value of 2.2 mg/day, while a value of 1.4 mg/day was obtained by downward extrapolation of the AI for adults using body weight to the power of 0.75 and respective reference weights (allometric scaling) and allowing for growth needs by addition of a growth factor; thus, an AI of 1.8 mg/day was set for infants aged 7-12 months, being the mean of both values.

The German-speaking countries derived AIs for children by interpolation between the values for infants and adults (D-A-CH, 2013), while Afssa (2001) estimated it based on the AI set for adults and correcting for the energy requirements of the respective age groups.

IOM (1998) extrapolated the AIs for children and adolescents from the AI of adults using allometric scaling and allowing for growth needs by the addition of a growth factor, which resulted in values consistent with available observed intakes for these age groups and intakes associated with blood and urinary pantothenic acid concentrations considered adequate (i.e. falling in typically observed ranges).

4.3. Pregnancy and lactation

The German-speaking countries (D-A-CH, 2013), Afssa (2001) and the UK COMA (DH, 1991) considered the AI set for adults to be sufficient to cover the period of pregnancy. WHO/FAO (2004) and IOM (1998) noted some evidence of lower whole blood pantothenic acid concentrations in pregnant women compared to non-pregnant women, although no differences in urinary excretion were observed and average intakes were found to exceed excretion (Song et al., 1985). The IOM (1998) set an AI of 6 mg/day based on observed average intakes in pregnant women (Song et al., 1985) and rounding up.

WHO/FAO (2004), Afssa (2001) and IOM (1998) proposed an AI of 7 mg/day for lactating women, to compensate for losses through breast milk. D-A-CH (2013) and the UK COMA (DH, 1991) considered the AI set for adults to be sufficient to cover the period of lactation.

Table 1: Overview of Dietary Reference Values for pantothenic acid

	D-A-CH (2013)	WHO/FAO (2004)	Afssa (2001)	IOM (1998)	SCF (1993)	DH (1991)
Infants						
Age (months)	< 4	0–6	-	0–6	-	-
AI (mg/day)	2	1.7		1.7		
Age (months)	4–<12	7–12	0–12	7–12	-	-
AI (mg/day)	3	1.8	2	1.8		
Children and adolescents						
Age (years)	1–<4	1–3	1–3	1–3	-	-
AI (mg/day)	4	2	2.5	2		
Age (years)	4–<7	4–6	4–6	4–8	-	-
AI (mg/day)	4	3	3	3		
Age (years)	7–<10	7–9	7–9	9–13	-	-
AI (mg/day)	5	4	3.5	4		
Age (years)	10–<13	10–18	10–12	14–18	-	-
AI (mg/day)	5	5	4	5		
Age (years)	13–<19	-	13–15	-	-	-
AI (mg/day)	6		4.5			
Age (years)	-	-	16–19	-	-	-
AI (mg/day)			5			
Adults						
Age (years)	≥ 19	≥ 19	≥ 19	≥ 19	≥ 19	≥ 19
AI (mg/day)	6	5	5	5	3–12 [(a)]	3–7 [(a)]
Pregnancy						
AI (mg/day)	6	6	5	6	3–12 [(a)]	3–7 [(a)]
Lactation						
AI (mg/day)	6	7	7	7	3–12 [(a)]	3–7 [(a)]

(a): Acceptable Range of Intakes.

5. Criteria (endpoints) on which to base Dietary Reference Values

5.1. Indicators of pantothenic acid requirement

The Panel considers that there is no suitable biomarker available to derive the AR for pantothenic acid.

5.2. Pantothenic acid intake and health consequences

Data examining the relationship between pantothenic acid intake and health outcomes are scarce.

A comprehensive search of the literature published between January 1990 and December 2011 was performed as preparatory work to this assessment to identify relevant health outcomes upon which DRVs may potentially be based for pantothenic acid (El-Sohemy et al., 2012). Five observational studies were retrieved, which considered the relationship between pantothenic acid intake to health outcomes including genome instability (one cross-sectional study by Fenech et al. (2005)), birth outcomes (two prospective studies (Lagiou et al., 2005; Haggarty et al., 2009)), blood pressure (one cross-sectional study by Schutte et al. (2003)), and Parkinson’s disease (one case-control study by Hellenbrand et al. (1996)).

The Panel considers that the data available from these studies are very limited and cannot be used for deriving DRVs for pantothenic acid.

5.3. Specific considerations during pregnancy and lactation

Two small cohort studies in pregnant and lactating women and non-pregnant, non-lactating women provide data on pantothenic acid intakes as well as urinary pantothenic acid excretion (Song et al., 1985; Shibata et al., 2013) and whole blood pantothenic acid concentration (Song et al., 1985). Mean pantothenic acid intakes were between 5.3 and 6.2 mg/day in pregnant and lactating women and 4.8 and 5.0 mg/day in controls. In both studies, average urinary pantothenic acid excretion levels were lower than intakes in all groups of women. Results were inconsistent with respect to differences in urinary excretion of pantothenic acid between pregnant or lactating and non-pregnant, non-lactating women. Song et al. (1985) observed that whole blood concentrations of pantothenic acid were significantly lower in pregnant and lactating women compared to non-pregnant, non-lactating women, as well as in pregnant women compared to lactating women. The Panel concludes that data on biomarkers in pregnant and lactating women are scarce and provide inconsistent results and cannot be used to infer on a difference in pantothenic acid status of pregnant and lactating women compared to non-pregnant, non-lactating women.

Assuming an average breast milk pantothenic acid concentration of 2.5 mg/L (see Section 2.2.) and an average breast milk secretion of 0.8 L/day over the first six months of lactation (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the Panel notes that mean pantothenic acid secretion in milk is 2 mg/day in fully breastfeeding women.

6. Data on which to base Dietary Reference Values

The Panel considers that the available data are insufficient to derive ARs and PRIs for pantothenic acid, and therefore proposes to set an AI for all population groups. The setting of an AI for pantothenic acid is based on observed pantothenic acid intakes with a mixed diet and the apparent absence of signs of deficiency in the EU, suggesting that current intake levels are adequate. There is no indication that the AI should be different according to sex.

6.1. Adults

The Panel decided to use the approximate midpoint of the observed median/mean intakes (Appendices C and D) to set an AI at 5 mg pantothenic acid per day for adults of all ages.

6.2. Infants, children and adolescents

Assuming an average breast milk pantothenic acid concentration of 2.5 mg/L (Section 2.2.) and an average breast milk intake of exclusively breast-fed infants aged zero to six months of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the estimated intake of infants aged zero to six months is about 2 mg/day. The AI for infants over six months of age can be derived by extrapolation from this figure, using allometric scaling based on reference body weights of the respective age groups,[8] to the power of 0.75, in order to account for the role of pantothenic acid in energy metabolism, and rounding to the nearest unit. The AI for infants aged 7–11 months is set at 3 mg/day.

[8] Mean of body weight-for-age at 50th percentile of male and female infants aged three and nine months (WHO Multicentre Growth Reference Study Group (World Health Organization), 2006. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. 312 pp.).

The Panel sets an AI for pantothenic acid of 4 mg/day for young and older children and of 5 mg/day for adolescents (Table 2), based on the approximate midpoints of the observed median/mean intakes of the respective age groups (Appendix B).

6.3. Pregnancy and lactation

The Panel considers that data are insufficient to derive a specific AI for pantothenic acid in pregnancy. The Panel considers that the AI for adults of 5 mg/day also applies to pregnant women.

Considering average pantothenic acid losses through breast milk of 2 mg/day during lactation (Section 5.3.), the Panel proposes to increase the AI for lactating women to 7 mg/day.

CONCLUSIONS

The Panel concludes that there is insufficient evidence to derive an Average Requirement (AR) and a Population Reference Intake (PRI) for pantothenic acid. Suitable data on pantothenic acid intake or status and health outcomes were not available for the setting of DRVs for pantothenic acid. Thus, the Panel proposes an Adequate Intake (AI) for adults based on observed intake data. It was considered unnecessary to give sex-specific values. The Panel proposes that the adult AI also applies to pregnant women. For lactating women, an increment in the adult AI is proposed, in order to compensate for pantothenic acid losses through secretion of breastmilk. An AI is also proposed for infants aged 7–11 months based on extrapolation from the estimated intake of infants aged zero to six months using allometric scaling, and for children and adolescents based on observed intake data.

Table 2: Summary of Adequate Intakes for pantothenic acid

Age	Adequate Intake (mg/day)
7–11 months	3
1–3 years	4
4–10 years	4
11–17 years	5
≥ 18 years [(a)]	5
Lactation	7

(a): including pregnancy

RECOMMENDATIONS FOR RESEARCH

The Panel recommends further research on pantothenic acid biomarkers that could be used to characterise the adequacy of pantothenic acid status in relation to physiological functions of the vitamin and allow the estimation of pantothenic acid requirements in various population groups.

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APPENDICES

Appendix A. Pantothenic acid concentration of human milk from healthy mothers

Reference	Number of women (number of samples)	Country	Total maternal intake (mg/day)	Stage of lactation	Pantothenic acid concentration (mg/L)		Method of analysis
			mean		mean ± SD	range	
DHSS (1977) (as reported by Picciano (1995))	96 (pooled sample from five cities)	UK	Not reported	Not reported	2.2	n.a.	Not reported
Ford et al. (1983)	35	UK	Not reported [(a)]	1–5 days	1.26	0.48–1.80	'Standard microbiological methods'
				6–15 days	2.07	0.42–3.23	
				16–244 days	2.61	1.80–3.70	
Sakurai et al. (2005)	(6)	Japan	Not reported [(b)]	6–10 days	2.0 ± 1.0	n.a.	Microbiological assay (*Lactobacillus arabinosus*)
	(6)			11–20 days	2.6 ± 0.8		
	(44)			21–89 days	2.9 ± 0.8		
	(34)			90–180 days	2.8 ± 1.1		
	(34)			181–365 days	2.6 ± 0.8		
	(57)			Summer	2.6 ± 0.9		
	(67)			Winter	2.8 ± 0.9		
	(119)			Overall	2.7 ± 0.9		
Johnston et al. (1981)	22	USA	5.4–26.6 [(c)]			1.8–16.7	Microbiological assay (*Lactobacillus plantarum*)
	(13)			1 month	7.1		
	(14)			2 months	7.6		
	(16)			3 months	6.6		
	(14)			4 months	6.8		
	(12)			5 months	6.1		
	(11)			6 months	5.8		
				Overall	6.7		
Song et al. (1984)	26	USA	5.9 ± 2.0 [(d)] 32.4 ± 24.6 [(e)]			n.a.	Radioimmunoassay
	(22)			2 weeks	2.57 ± 0.60		
	(24)			3 months	2.55 ± 0.73		

(a): No indication of supplementation
(b): Not taking supplements
(c): Three mothers were taking supplements at one month, two at two months, one at four months, none at five months and two at six months. Over the six months of the study, 5.4 mg/day is the lowest mean provided by diet alone, while 26.6 mg/day is the highest mean provided by diet and supplements.

(d): Not taking supplements (n = 46)
(e): Taking supplements (n = 6)
n.a., not available.

Appendix B. Pantothenic acid intake among children and adolescents in European countries

Country	Reference	Dietary assessment method (year of survey) [(a)]	Age (years)	n	Mean (mg/day)	SD	Median (mg/day)	P5 – P95
Boys						n.a.	n.a.	n.a.
Austria	Elmadfa et al. (2009)	Seven-day record (2003)	7–9	n.a.	4.0	n.a.	n.a.	n.a.
			10–12	n.a.	4.0	n.a.	n.a.	n.a.
			13–15	n.a.	4.0	n.a.	n.a.	n.a.
		Three-day record (2007–2008)	7–9	148	4.0	n.a.	n.a.	n.a.
			10–12	155	4.0	n.a.	n.a.	n.a.
			13–15	86	4.0	n.a.	n.a.	n.a.
		24-hour recall (2004) (Berufsschüler/AHS-schüler)	14–19	35/47	6.0/5.0	n.a.	n.a.	n.a.
France	Afssa (2009)	Seven-day record (2006–2007)	3–10	n.a.	4.7	1.7	4.6	n.a.
			11–14	n.a.	5.5	1.6	5.2	n.a.
			15–17	n.a.	5.5	1.6	5.2	n.a.
Germany	Mensink et al. (2007)	Three-day record (2006)	6–11	626	n.a.	n.a.	4.3	2.6–8.7
	Mensink et al. (2007)	Dietary history (over the last four weeks) (2006)	12–17	622	n.a.	n.a.	7.2	3.5–17.4
	DGE (2012)	Two non-consecutive 24-hour recalls (2005–2006)	15–19	506	n.a.	n.a.	4.0	
Ireland	IUNA (online-b)	Seven-day record (2003–2004)	5–8	145	5.4	2.2	5.1	2.6–9.8
	IUNA (online-b)	Seven-day record (2003–2004)	9–12	148	5.9	2.3	5.7	2.6–10.5
	IUNA (online-c)	Seven-day record (2005–2006)	13–14	95	7.0	3.9	5.9	3.3–13.0
	IUNA (online-c)	Seven-day record (2005–2006)	15–17	129	7.5	4.3	6.6	3.0–15.0
Girls								
Austria	Elmadfa et al. (2009)	Seven-day record (2003)	7–9	n.a.	3.6	n.a.	n.a.	n.a.
			10–12	n.a.	3.8	n.a.	n.a.	n.a.
			13–15	n.a.	3.4	n.a.	n.a.	n.a.
		Three-day record (2007–2008)	7–9	175	3.3	n.a.	n.a.	n.a.
			10–12	152	3.3	n.a.	n.a.	n.a.
			13–15	64	3.0	n.a.	n.a.	n.a.
		24-hour recall (2004) (Berufsschüler/AHS-schüler)	14–19	28/39	4.0/4.0	n.a.	n.a.	n.a.
France	Afssa (2009)	Seven-day record (2006–2007)	3–10	n.a.	4.2	1.2	3.9	n.a.
			11–14	n.a.	4.5	1.3	4.5	n.a.
			15–17	n.a.	4.3	1.4	4.0	n.a.
Germany	Mensink et al. (2007)	Three-day record (2006)	6–11	608	n.a.	n.a.	4.0	2.0–7.8
	Mensink et al. (2007)	Dietary history (over the last four weeks) (2006)	12–17	650	n.a.	n.a.	5.5	2.7–16.9
	DGE (2012)	Two non-consecutive 24-hour recalls (2005–2006)	15–19	536	n.a.	n.a.	3.1	
Ireland	IUNA (online-b)	Seven-day record (2003–2004)	5–8	151	4.7	1.8	4.4	2.5–7.8

	IUNA (online-b)	Seven-day record (2003–2004)	9–12	150	5.1	3.8	4.5	2.3–9.0
	IUNA (online-c)	Seven-day record (2005–2006)	13–14	93	5.1	3.6	4.2	1.8–10.8
	IUNA (online-c)	Seven-day record (2005–2006)	15–17	124	5.3	4.2	4.4	1.8–11.1
Both sexes								
Ireland	IUNA (online-a)	Four-day weighed dietary record (2010–2011)	1–4	500	4.5	1.8	4.1	2.4–8.0

(a): supplements excluded
n.a., not available

590 **Appendix C. Pantothenic acid intake among adults aged ~ 19–65 years in European countries**

Country	Reference	Dietary assessment method (year of survey)(a)	Age (years)	n	Mean (mg/day)	SD	Median (mg/day)	P5 – P95
Men								
Austria	Elmadfa et al. (2009)	24-hour recall	18–25	93	5.4	n.a.	n.a.	n.a.
			25–51	541	4.7	n.a.	n.a.	n.a.
			51–64	144	4.6	n.a.	n.a.	n.a.
France	Afssa (2009)	Seven-day record (2006–2007)	18–34	n.a.	6.0	2.1	5.8	n.a.
			35–54		6.6	1.9	6.3	n.a.
Germany	DGE (2012)	Two non-consecutive 24-hour recalls (2005–2006)	19–24	469	n.a.	n.a.	4.2	n.a.
			25–34	614	n.a.	n.a.	4.4	n.a.
			35–50	1 946	n.a.	n.a.	4.5	n.a.
			51–64	1 460	n.a.	n.a.	4.5	n.a.
Hungary	Zajkas et al. (2007)	Three-day record (2003–2004)	18–34	473	4.0	1.2	n.a.	n.a.
			35–59	136	4.1	1.2	n.a.	n.a.
Ireland	IUNA (2011)	Four-day record (2008–2010)	18–64	634	6.8	2.5	6.3	3.5–11.8
Portugal	Lopes et al. (2006)	Food frequency questionnaire (1999–2003). *Data collected in Porto*	18–64	917	4.8	1.2	n.a.	3.0–7.0
Women								
Austria	Elmadfa et al. (2009)	24-hour recall	18–25	187	4.1	n.a.	n.a.	n.a.
			25–51	959	4.4	n.a.	n.a.	n.a.
			51–64	199	4.5	n.a.	n.a.	n.a.
France	Afssa (2009)	Seven-day record (2006–2007)	18–34	n.a.	4.7	1.4	4.6	n.a.
			35–54		5.3	1.4	5.2	n.a.
Germany	DGE (2012)	Two 24-hour recalls (2005–2006)	19–24	486	n.a.	n.a.	3.3	n.a.
			25–34	852	n.a.	n.a.	3.6	n.a.
			35–50	2 648	n.a.	n.a.	3.7	n.a.
			51–64	1 740		n.a.	3.6	n.a.
Hungary	Zajkas et al. (2007)	Three-day record (2003–2004)	18–34	176	3.2	0	n.a.	n.a.
			35–60	295	3.2	0	n.a.	n.a.
Ireland	IUNA (2011)	Four-day record (2008–2010)	18–64	640	5.0	1.9	4.7	2.4–8.2
Portugal	Lopes et al. (2006)	Food frequency questionnaire (1999–2003). *Data collected in Porto*	18–64	1 472	4.7	1.3	n.a.	2.8–7.0

Both sexes								
Latvia	Joffe et al. (2009)	Two non-consecutive 24-hour dietary recalls + food frequency questionnaire (2008)	17–26	378	4.6	n.a.	n.a.	n.a.
			27–36	206	4.8	n.a.	n.a.	n.a.
			37–46	272	4.6	n.a.	n.a.	n.a.
			47–56	304	4.7	n.a.	n.a.	n.a.
			57–64	217	4.3	n.a.	n.a.	n.a.

(a): supplements excluded
n.a., not available

Appendix D. Pantothenic acid intake among adults aged ~65 years and over in European countries

Country	Reference	Dietary assessment method (year of survey)(a)	Age (years)	n	Mean (mg/day)	SD	Median (mg/day)	P5 – P95
Men								
Austria	Elmadfa et al. (2009)	Three-day record (2007–2008)	≥ 55	121	3.8	n.a	n.a	n.a
France	Afssa (2009)	Seven-day record (2006–2007)	55–79	n.a.	6.2	1.8	6.0	n.a.
Germany	DGE (2012)	Two non-consecutive 24-hour recalls (2005–2006)	65–80	1 165	n.a.	n.a.	4.2	n.a.
Hungary	Zajkas et al. (2007)	Three-day record (2003–2004)	≥ 60	138	3.5	1.2	n.a.	n.a.
Ireland	IUNA (2011)	Four-day record (2008–2010)	≥ 65	106	6.0	1.9	5.7	3.1–9.0
Poland	Przysławski (1999)	24-hour recall (1996–1997)	≥ 50	443	2.6	1.3	n.a.	n.a.
Portugal	Lopes et al. (2006)	Food frequency questionnaire (1999–2003). *Data collected in Porto*	≥ 65	246	4.7	1.2	n.a.	3.0–6.8
Women								
Austria	Elmadfa et al. (2009)	Three-day record (2007–2008)	≥ 55	302	3.7	n.a	n.a	n.a
France	Afssa (2009)	Seven-day record (2006–2007)	55–79	n.a.	5.1	1.3	4.9	n.a.
Germany	DGE (2012)	Two non-consecutive 24-hour recalls (2005–2006)	65–80	1 331	n.a.	n.a.	3.6	n.a.
Hungary	Zajkas et al. (2007)	Three-day record (2003–2004)	≥ 60	235	2.9	1.1	n.a.	n.a.
Ireland	IUNA (2011)	Four-day record (2008–2010)	≥ 65	120	5.3	1.9	5.2	2.8–9.8
Poland	Przysławski (1999)	24-hour recall (1996–1997)	≥ 50	803	2.2	0.9	n.a.	n.a.
Portugal	Lopes et al. (2006)	Food frequency questionnaire (1999–2003). *Data collected in Porto*	≥ 65	339	4.4	1.2	n.a.	2.6–6.5

(a): supplements excluded
n.a., not available;

597 ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
Anses	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement, et du travail
AR	Average Requirement
CIQUAL	Centre d'Information sur la Qualité des Aliments
CoA	Coenzyme A
COMA	Committee on Medical Aspects of Food Policy
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DGE	Deutsche Gesellschaft für Ernährung
DH	Department of Health
DRV	Dietary Reference Value
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
FSA	Food Standards Agency
IOM	U.S. Institute of Medicine of the National Academy of Sciences
IUNA	Irish Universities Nutrition Alliance
IUPAC	International Union of Pure and Applied Chemistry
NNR	Nordic Nutrition Recommendations
SCF	Scientific Committee for Food
SD	Standard Deviation
UL	Tolerable Upper Intake Level
UNU	United Nations University
WHO	World Health Organization

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