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SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for niacin[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for niacin. Niacin is a generic term for nicotinic acid and nicotinamide. Niacin can be synthesised in the human body from the indispensable amino acid tryptophan. Approximately 60 mg of tryptophan yields 1 mg of niacin defined as 1 mg niacin equivalent (NE). Long-term inadequate intake of tryptophan and niacin can lead to the development of pellagra. In the absence of new scientific data, the Panel endorses the Average Requirement (AR) for adults of 1.3 mg NE/MJ (5.5 mg NE/1 000 kcal) adopted by the Scientific Committee for Food (1993), based on data on urinary excretion of niacin metabolites as an endpoint. The Population Reference Intake (PRI) of 1.6 mg NE/MJ (6.6 mg NE/1 000 kcal) is derived from the AR assuming a coefficient of variation of 10 %. For infants aged 7-11 months, children and adolescents, as well as for pregnant and lactating women, the Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement differs from that of adults; therefore, the AR and PRI for adults are also applied to these age and life stage groups.

KEY WORDS

niacin, nicotinic acid, nicotinamide, tryptophan, urinary excretion, Dietary Reference Value

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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 for the European population, including niacin.

Niacin is a generic term for nicotinic acid and nicotinamide, soluble organic compounds that belong to the group of B vitamins. Niacin is found in a wide range of foods. Main food groups contributing to niacin intakes of adults include meat and meat products, grains and grain-based products and milk and milk products. Depending on the foodstuff, the mean absorption of niacin is from about 23 % to about 70 %; it is lowest from cereals and highest from animal products. Niacin can be synthesised in the human body from the indispensable amino acid tryptophan. Approximately 60 mg of tryptophan yields 1 mg of niacin defined as 1 mg niacin equivalent (NE). Inadequate iron, riboflavin or vitamin B6 status decreases the conversion of tryptophan to niacin.

In vivo nicotinic acid is converted to nicotinamide, which is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are essential to cells and involved in many biochemical reactions. Niacin circulates in the plasma as nicotinamide and nicotinic acid. Both forms are transported to cells and tissues, which they enter by diffusion to perform the intracellular functions of niacin. Niacin is trapped within the cell as NAD or NADP.

The major pathway of catabolism of nicotinic acid and nicotinamide is by methylation in the liver to *N*-methyl-nicotinamide (NMN) and subsequent oxidation to *N*-methyl-2-pyridone-carboxamide (2-Pyr) and *N*-methyl-4-pyridone-carboxamide (4-Pyr). In humans, the two major excretion products are NMN and 2-Pyr, which under normal conditions represent about 20-35 % and 45-60 % of niacin metabolites, respectively. The amount of niacin metabolites excreted depends on the niacin and tryptophan intake. Long-term inadequate intake of tryptophan and niacin results in reduced urinary excretion of niacin metabolites, and can lead to the development of pellagra. Based on experimental studies on niacin deficiency, it is recognised that niacin requirement is strongly dependent on energy intake. No signs of niacin deficiency were observed in subjects on diets containing at least approximately 1 mg NE/MJ (4.4 mg NE/1 000 kcal), while providing no less than 8.4 MJ/day (2 000 kcal/day). Diets providing at least 1.3 mg NE/MJ (5.5 mg NE/1 000 kcal) were sufficient to prevent depletion and maintain niacin body stores, as indicated by a sharp increase in urinary excretion of niacin metabolites above this intake.

The Panel notes that no new scientific data that would necessitate an amendment of the DRVs for niacin have become available since the publication of the Scientific Committee for Food (SCF) report in 1993. The Panel therefore endorses the relationship proposed by SCF (1993) between niacin requirement and energy requirement.

The Panel endorses the Average Requirement (AR) for adults (men and women) of 1.3 mg NE/MJ (about 5.5 mg NE/1 000 kcal) and the Population Reference Intake (PRI) of 1.6 mg NE/MJ (about 6.6 mg NE/1 000 kcal) adopted by SCF (1993) assuming a coefficient of variation of 10 %. The Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement for infants aged 7-11 months, children and adolescents differs from that of adults. Therefore, the AR and PRI for adults are applied to these age groups as well. The Panel also considers that, in pregnant and lactating women, there is no evidence that the relationship between niacin requirement and energy requirement differs from that of other adults. Therefore, the AR and PRI for adults are applied to these life stage groups. Taking into account the reference energy intake, i.e. the AR for energy for various Physical Activity Levels (PAL values), the intake of NE/MJ is also expressed as mg NE/day. The Panel notes that, as for other nutrient reference values, DRVs for niacin are set under the assumption that intakes of other essential nutrients, particularly iron, riboflavin, vitamin B6 and protein, and energy are adequate.

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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,[5] 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;

[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.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1-24.

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

Niacin is a generic term for nicotinic acid and nicotinamide, which are water-soluble organic compounds that belong to the group of B vitamins. Both compounds are identical in their vitamin function. Niacin can be obtained from food as well as being produced in the liver from the indispensable amino acid tryptophan.

In 1993, the Scientific Committee for Food (SCF) adopted an opinion on nutrient and energy intakes for the European Community (SCF, 1993). For niacin, SCF set Population Reference Intakes (PRIs) for adults and children, as well as an Average Requirement (AR) and a Lowest Threshold Intake (LTI) for adults.

2. Definition/category

Nicotinic acid has a molecular mass of 123.11 Da and nicotinamide has a molecular mass of 122.11 Da. Nicotinamide is more soluble in water than nicotinic acid. Nicotinamide is a constituent of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Both of these can accept a hydrogen ion (H^+) and two electrons (namely a hydride anion, H^{-1}) to form NADH and NADPH, and may be involved in redox reactions as electron acceptors (NAD, NADP) or donors (NADH, NADPH).

2.1. Functions of niacin

2.1.1. Biochemical functions

The function of niacin is as the precursor of the nicotinamide nucleotide coenzymes NAD and NADP, which are involved in oxidation/reduction reactions and associated with both catabolic and anabolic processes.

Many dehydrogenases use NAD or NADP or both. Generally, NAD-linked dehydrogenases catalyse redox reactions of the oxidative pathways of metabolism, particularly in glycolysis, the citric acid cycle and the respiratory chain of mitochondria. NADP-linked dehydrogenases are characteristically found in reductive biosynthesis, as in the pathway of fatty acid and steroid synthesis, and also in the pentose-phosphate pathway. Therefore, NAD is essential for energy-producing reactions and NADP for anabolic reactions. NAD also participates in unique non-redox adenosine diphosphate–ribose transfer reactions involved in protein modification, calcium mobilisation, cell signaling and DNA repair (Kim et al., 1993; Malanga and Althaus, 2005; Sauve et al., 2006; Belenky et al., 2007; Bogan and Brenner, 2008; Kirkland, 2014).

2.1.2. Health consequences of deficiency and excess

2.1.2.1. Deficiency

Long-term inadequate intake of tryptophan and niacin can lead to the development of pellagra. The common symptoms of pellagra include photosensitive dermatitis, skin lesions, tongue and mouth soreness, vomiting, diarrhoea, depression and dementia. Early symptoms are usually non-specific and include weakness, loss of appetite, fatigue, digestive disturbances, abdominal pain and irritability. Untreated pellagra results in death from multiorgan failure (Hegyi et al., 2004; Wan et al., 2011).

In industrialised countries, pellagra is rare. It may be observed when conditions or diseases interfere with niacin intake, absorption and/or metabolism, e.g. in chronic alcohol abuse or in patients with anorexia nervosa or gastrointestinal diseases characterised by malabsorption or disturbances in tryptophan metabolism (Wan et al., 2011).

2.1.2.2. Excess

The Tolerable Upper Intake Level (UL) for free nicotinic acid is 10 mg/day, and the UL for nicotinamide is 900 mg/day in adults (SCF, 2002). These ULs are not applicable during pregnancy or lactation because of insufficient data.

The UL for nicotinic acid is based on data indicating occasional flushing at an intake of 30 mg/day (Sebrell and Butler, 1938), using an uncertainty factor of three to allow for the fact that a slight effect (occasional flushing) was reported and that the study was performed in a small number of subjects but taking into account the steep dose–response relationship. For nicotinamide, the No Observed Adverse Effect Level (NOAEL) of 25 mg/kg body weight per day reported in patients with diabetes (Pozzilli et al., 1995) was used, and an uncertainty factor of two was applied to allow for the fact that adults may eliminate nicotinamide more slowly than the study groups, many of which were children.

2.2. Physiology and metabolism

2.2.1. Intestinal absorption

Intestinal absorption of nicotinic acid and nicotinamide supplied from food is mediated by sodium ion-dependent, carrier-mediated diffusion, but a role for the human organic anion transporter 10 (hOAT10) and the intracellular protein–tyrosine kinase pathway has also been proposed (Evered et al., 1980; Nabokina et al., 2005; Said et al., 2007; Bahn et al., 2008; Said, 2011).

Depending on the foodstuff, the mean absorption of niacin is from about 23 % to 70 %; it is lowest from cereals and highest from animal products (Carter and Carpenter, 1982; Wei, 1982; Wall et al., 1987). In order to be absorbed, NAD and NADP from the diet need to be hydrolysed in the intestine into nicotinamide (Henderson, 1983; Gropper et al., 2009). In cereals, niacin is mostly present as esterified forms unavailable for absorption, namely niacytin consisting of nicotinic acid esterified to polysaccharides, and also to polypeptides and glycopeptides (niacinogenes) (Wall et al., 1987; Ball, 1998). The majority (about 75 %) of this bound nicotinic acid is biologically unavailable after cooking and only a small part (less than about 25 %) of these bound forms may become hydrolysed by gastric acid (Carter and Carpenter, 1982). The bioavailability of bound forms of niacin can be increased by pretreatment of the food with alkali for ester bond hydrolysis (Mason et al., 1973; Carter and Carpenter, 1982; Carpenter and Lewin, 1985).

2.2.2. Transport in blood and distribution to tissues

Niacin circulates in the plasma as nicotinamide and nicotinic acid (Pollak et al., 2007; Kirkland, 2009). Nicotinamide is the major form of niacin found in the bloodstream (Kirkland, 2009). From the blood, nicotinic acid and nicotinamide move across cell membranes by simple diffusion; however, the transport into the kidney tubules and erythrocytes requires a carrier (Henderson, 1983; Gropper et al., 2009).

2.2.3. Metabolism

Niacin can be synthesised in the human body from the indispensable amino acid tryptophan. Approximately 60 mg of tryptophan yields 1 mg of niacin, as reviewed by Horwitt et al. (1981);

because of this conversion ratio, 60 mg of tryptophan has been defined as 1 mg niacin equivalent (NE). The conversion of tryptophan to niacin depends on tryptophan intake rather than on niacin status; when dietary tryptophan is limited, the efficiency of conversion of tryptophan to niacin falls below the commonly used conversion ratio, because of the priority for the use of dietary tryptophan in protein synthesis (Vivian et al., 1958; Patterson et al., 1980; Bender, 2003; Kirkland, 2007). Inadequate iron, riboflavin, or vitamin B6 status decreases the conversion of tryptophan to niacin (McCormick, 1989). Inter-individual differences (about 30 %) in the conversion efficiency of tryptophan to niacin have been reported (Patterson et al., 1980; Horwitt et al., 1981). The conversion of tryptophan to niacin is more efficient in pregnant women than in other adults (Wertz et al., 1958); this is supported by data collected during pregnancy in animals (Ftukijwatari et al., 2004). However, the tryptophan to niacin conversion ratio would need to be confirmed by other studies in pregnant women. The conversion of tryptophan to niacin is reduced under certain conditions such as carcinoid syndrome and as a result of decreased absorption of tryptophan in Hartnup's disease and other conditions associated with malabsorption, as well as prolonged treatment with certain drugs (Hegyi et al., 2004; Wan et al., 2011).

Within the cell, niacin is used to synthesise NAD, which can then be phosphorylated to NADP, and both of these can accept two electrons and one proton to form NADH and NADPH. Humans use both nicotinamide and nicotinic acid to synthesise NAD but utilise different pathways to achieve this (Bogan and Brenner, 2008; Sauve, 2008; Kirkland, 2009). Nicotinamide is converted to NAD by reaction with 5-phosphoribosyl-1-pyrophosphate and ATP. Nicotinic acid reacts with 5-phosphoribosyl-1-pyrophosphate and forms the nicotinic acid mononucleotide, which is then transformed into nicotinic acid dinucleotide by adenylation, and subsequently converted to NAD by amidation in the presence of glutamine (Bogan and Brenner, 2008; Sauve, 2008; Kirkland, 2009). NAD is converted to NADP by reaction with ATP. Intracellular concentrations of NAD are generally higher than NADP concentrations (Srikantia et al., 1968; Fu et al., 1989; Sauve, 2008; Gropper et al., 2009; Kirkland, 2009).

The major pathway of catabolism of nicotinic acid and nicotinamide is by methylation in the liver and subsequent oxidation. Both compounds are metabolised to *N*-methyl-nicotinamide (NMN) with the participation of ATP and Mg^{2+} and *S*-adenosylmethionine as a methyl donor. NMN can be oxidised to *N*-methyl-2-pyridone-carboxamide (2-Pyr)[6] and *N*-methyl-4-pyridone-carboxamide (4-Pyr) (Bender, 2003), which are found in both plasma and urine (see Sections 2.2.4.1. and 2.3.).

2.2.4. Elimination

The main route of niacin excretion is via the urine. There is no indication that faeces constitute an important route of excretion for absorbed niacin.

2.2.4.1. Urine

Once niacin is absorbed, niacin metabolites are excreted in urine. In humans the two major excretion products of niacin catabolism are NMN and 2-Pyr, which under normal conditions represent, respectively, about 20-35 % and 45-60 % of niacin metabolites in urine (Mrochek et al., 1976; Shibata and Matsuo, 1989; Gropper et al., 2009). Small amounts of 4-Pyr (about 6-9 % of niacin metabolites) are also excreted. The amount of niacin metabolites excreted depends on the niacin and tryptophan intake (see Sections 2.3 and 5.1.) (Goldsmith et al., 1952; Goldsmith et al., 1955; Horwitt et al., 1956; Jacob et al., 1989). Humans suffering from niacin deficiency have reduced renal excretion of metabolites (Goldsmith et al., 1955; Hegyi et al., 2004). Elevated urinary excretion of NMN and/or 2-Pyr has been observed in pregnant women compared with non-pregnant women and in women

[6] *N*-methyl-2-pyridone-carboxamide has also been referred to as 6-pyridone in some papers; in this Opinion the term 2-Pyr will be used consistently to refer to this compound.

compared with men, as well as in women taking oral contraceptives compared with control women (Horwitt et al., 1975). Urinary excretion of niacin metabolites was found to increase from early to late pregnancy and decline after childbirth (Wertz et al., 1958; Ftukijwatari et al., 2004).

2.2.4.2. Breast milk

Lactating women secrete niacin (nicotinamide and nicotinic acid) via their breast milk (Greer, 2001). Niacin concentrations in human milk from healthy mothers in the EU sampled at various stages of lactation are listed in Appendix A. Owing to the high protein turnover and the net positive nitrogen retention in infancy, tryptophan concentration in breast milk and its conversion to niacin by infants is not considered in this Section or in Appendix A. Using two UK studies (DHSS, 1977; Ford et al., 1983), the mean concentration of niacin in mature human milk was about 2.1 mg/L. The niacin concentration in breast milk is reported to be dependent on maternal NE intake (Picciano, 2001). Considering a mean milk transfer of 0.8 L/day during the first six months of lactation in exclusively breastfeeding women (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), and the mean concentration of niacin in mature human milk in the EU of about 2.1 mg/L, secretion of preformed niacin into milk during lactation is about 1.7 mg/day.

2.3. Biomarkers

2.3.1. Urinary niacin metabolites

A significant linear correlation was observed between 24-hour urinary excretion of NMN, 2-Pyr, 4-Pyr or the sum of the three metabolites and usual dietary intake of niacin and/or NE (mean intake of about 21-27 mg NE/day) in healthy men and women (18-27 years) (Shibata and Matsuo, 1989; Tsuji et al., 2010) and children (10-12 years) (Tsuji et al., 2011). A significant correlation between NE intakes and 24-hour urinary excretion of NMN and 2-Pyr (average of four days per subject) was also observed in three groups of young men (19-28 years) given 8 mg/day of niacin and different tryptophan doses (total intake of about 12-22 mg NE/day, each of the three doses being consumed for 35 days) (Patterson et al., 1980). A dose-response relationship between NE intake and urinary excretion of niacin metabolites has also been observed in girls aged 7-9 years receiving diets providing between about 1.1 and 3.1 mg NE/MJ (Moyer et al., 1963; Miller and Abernathy, 1965).

In seven healthy men on fixed diets containing between 6.1 and 32 mg NE/day during different study periods (one initial period of 13 days and three study periods of 35 or 15 days in which five study doses were tested), mean urinary excretion of 2-Pyr and NMN varied between about 1-20 mg/day and 0.8-5 mg/day according to the dose, respectively (Jacob et al., 1989). For each metabolite, group mean urinary concentrations (n = 5) assessed at the end of each study period were significantly linearly correlated with mean NE intake. Urinary NMN excretion, but not 2-Pyr, was significantly lower in subjects with an intake of 6.1-10.1 mg NE/day than in those with an intake of 19.2-19.6 mg NE/day.

A decrease in urinary excretion of the niacin metabolites NMN and 2-Pyr[7] in subjects consuming different levels of NE is indicative of depleted body stores of niacin (Goldsmith et al., 1952; Goldsmith et al., 1955). Goldsmith et al. (1952) reported that no signs of pellagra were observed in subjects whose urinary NMN excretion remained above 0.9 mg/day, while the excretion decreased to about 0.5-0.7 mg/day in subjects with pellagra.

The response of urinary excretion of niacin metabolites to oral test doses of nicotinamide may reflect niacin body stores. When an oral dose of nicotinamide (20 mg/70 kg body weight) was administered at the end of the initial period (19.6 mg NE/day), the "low" intake period (6.1-10.1 mg NE/day) and the "repletion" period (19.2 mg NE/day), urinary excretion of niacin metabolites assessed at one hour

[7] Referred to as 6-pyridone in the paper.

pre-dose, then hourly for four hours post-dose indicated that increases in urinary NMN excretion above baseline values were similar according to diets, while urinary 2-Pyr excretion over four hours post-dose was significantly greater on the baseline diet compared with the other diets (Jacob et al., 1989). In subjects with pellagra (Goldsmith et al., 1952), an increase in NMN excretion (from 0.5 to 2.4-3.9 mg/day) and 2-Pyr excretion (from 0 to 14.3-21.3 mg/day) was observed in response to oral test doses of nicotinamide (50 mg), while a slow increase in urinary excretion of niacin metabolites was observed following daily administration of 2 mg nicotinamide or 3 mg tryptophan for 20-90 days.

Niacin metabolites are excreted in the urine even at low NE intakes. For NE intakes above about 11 mg/day, urinary excretion of niacin metabolites increased sharply, which has been suggested to reflect saturation of body stores (Goldsmith et al., 1955).

The Panel notes that urinary excretion of niacin metabolites is considered as a marker of niacin status. However, there are only limited data available as to the suitability of urinary niacin metabolites as biomarkers of niacin intake.

2.3.2. Plasma niacin metabolites

In seven men consuming different amounts of NE (five study doses) (Jacob et al., 1989) (see Section 2.3.1.), there was a significant linear relationship between group means (n = 5) of plasma NMN concentration at the end of each study period and the corresponding NE intake, but the only significant difference was observed between "low" (6.1 and 10.1 mg NE/day) and "high" NE diets (32 mg NE/day). A decrease in plasma 2-Pyr concentration to undetectable levels was observed with the two "low" NE diets, but there was no significant linear relationship between group means of plasma 2-Pyr concentration and NE intakes.

The Panel notes that differences in plasma NMN concentrations reflect changes in niacin status associated with large changes in NE intake (6.1 to 32 mg NE/day) over periods of time. The Panel also notes that plasma niacin metabolites are less sensitive to changes in NE intakes than urinary metabolites. The Panel considers that the available data are too limited to judge on the suitability of plasma niacin metabolites as biomarker of niacin status.

2.3.3. Erythrocyte pyridine nucleotides

A decrease in NE intake is associated with a fall in whole blood pyridine nucleotide concentrations (Vivian et al., 1958). Fu et al. (1989) investigated the effect of varying NE intakes on erythrocyte NAD and NADP concentration. No significant difference in erythrocyte NAD concentration was observed between intakes of 6.1 and 10.1 mg NE/day after five weeks, but a significant decrease was observed compared with the initial intake of 19.6 mg NE/day. However, intakes of 25 and 32 mg NE/day did not significantly increase erythrocyte NAD after five weeks compared with the "repletion" intake of 19.2 mg NE/day. In contrast to erythrocyte NAD concentration, no significant change in erythrocyte NADP concentration was observed.

The Panel notes that erythrocyte NAD concentration may be a marker of niacin depletion caused by "low" NE intake (≤ 10.1 mg NE/day); however, based on the limited data available no conclusion can be drawn on the relationship between erythrocyte NAD concentration and niacin requirement.

3. Dietary sources and intake data

3.1. Dietary sources

Niacin is found in a wide range of foods. The main sources of niacin include liver, meat and meat products, fish, peanuts and whole grains. Foods rich in protein, such as milk, cheese and eggs, which are good sources of the amino acid tryptophan, are therefore good sources of NEs. Coffee is also a source of niacin. In uncooked animal food, niacin occurs mainly in the form of the nucleotides NAD and NADP, and in plant food it is mostly present as esterified forms that require hydrolysis, which can occur during the course of food preparation (see Section 2.2.1). Niacin is temperature resistant; however, significant amounts of niacin can be lost in cooking water that is discarded.

Currently, nicotinic acid and nicotinamide may be added to foods[8] and food supplements.[9] Inositol hexanicotinate (inositol hexaniacinate) may be added to food supplements[8] only. The niacin content of infant and follow-on formulae is regulated.[10]

3.2. Dietary intake

Dietary intakes of niacin were estimated by the Evidence Management Unit (DATA) of EFSA using the EFSA Comprehensive Food Consumption Database (EFSA, 2011b) and the EFSA Food Composition Database. This assessment includes food consumption data from 12 dietary surveys (Appendix B) from nine countries (Finland, France, Germany, Ireland, Italy, Latvia, the Netherlands, Sweden and the UK), which were either already classified, or re-classified (French and Italian data), according to the FoodEx2 food classification system (EFSA, 2011a). The EFSA Food Composition Database was compiled during a procurement project (Roe et al., 2013) involving fourteen national food database compiler organisations, who were allowed to borrow compatible data from other countries in case no original composition data were available. This assessment on niacin includes food composition information from Finland, France, Germany, Italy, the Netherlands, Sweden and the UK. The amount of borrowed total niacin contents in these datasets were 6.4 % for Germany, 91 % for the UK, and 100 % for the others. For Ireland and Latvia, respectively, the UK and German food composition data were used. Total niacin content was directly available for 1 806 food terms of the food consumption data used in this assessment, and was missing for all included countries for 503 food terms, to which either a value from another food (in case the food with missing value was consumed frequently or in high quantities or belonged to food groups with high concentration of niacin), or a zero value (otherwise), was attributed.

After consistency checks and replacement of missing values for total niacin in the EFSA Food Composition Database, total niacin intakes, i.e. including preformed niacin (nicotinamide and nicotinic acid) and tryptophan (tryptophan content divided by a factor of 60), were calculated in mg NE/MJ and mg NE/day, for males (Appendix C) and females (Appendix D). Niacin intake calculations were performed only on subjects with at least two reporting days. Food consumption data of infants (6-11 months), either formula-fed or breast-fed, were provided by three studies. Human milk consumption data were available from the Italian survey, or could be calculated from the available German data, but not for the Finnish survey, thus the contribution of human milk to total niacin intakes of infants was calculated for Italy and Germany. Food consumption data in children were provided by nine studies, and data on adults by eight studies, including one on pregnant women

[8] 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.

[9] 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.

[10] 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.

and adolescents. EFSA estimates are based on consumption of foods, either fortified or not (i.e. without dietary supplements).

Average total niacin intakes ranged from 2.1 to 3.5 mg NE/MJ (8-11 mg NE/day) in infants. For children and adolescents, they ranged from 2.7 to 4.0 mg NE/MJ (12-20 mg NE/day) (1-< 3 years), from 2.8 to 4.8 mg NE/MJ (14-32 mg NE/day) (3-< 10 years) and from 3.2 to 5.2 mg NE/MJ (25-41 mg NE/day) (10-< 18 years). In adults, average total niacin intakes ranged from 4.0 to 5.4 mg NE/MJ (27-53 mg NE/day), and ranges varied from 2.5-3.9 mg NE/MJ at the lower end (5^{th} percentile) to 5.9-7.7 mg NE/MJ at the upper end (95^{th} percentile) of the intake distributions (from 11.7-31.3 mg NE/day at the lower end to 37.3-78.2 mg NE/day at the upper end). Average daily intakes (but not energy-adjusted intakes) were slightly higher among males than females, mainly due to larger quantities of food consumed.

Main food groups contributing to niacin intakes were calculated for males (Appendix E) and females (Appendix F): they included meat and meat products, grains and grain-based products, milk and dairy products, as well as human milk and foods classified under 'food products for young population' for infants. Other important food groups contributing to niacin intake were composite dishes in Sweden and in the UK, fish and fish products among the elderly, especially in Sweden, coffee and cocoa beverages among Dutch, Finnish, Italian and Swedish adults, starchy roots or tubers and products thereof among Dutch children and adolescents, and alcoholic beverages in adult men in the UK, Ireland and the Netherlands. Differences in main contributors to niacin intakes between males and females were minor.

EFSA's niacin intake estimates in mg/day were compared with published intakes from the same surveys and datasets in German children (Kersting and Clausen, 2003; Mensink et al., 2007), Irish (IUNA, 2011), Finnish (Helldán et al., 2013) and Swedish (Amcoff et al., 2012) adults, and UK subjects (Bates et al., 2011) (Table 1). Among infants in the VELS study (Kersting and Clausen, 2003), the underestimation of, respectively, 19-24 % or 17-20 % in the average daily or energy-adjusted intakes could be due to differences in the nutrient compositions between the German and the EFSA databases. The overestimation of the Swedish intakes and underestimation of the UK intakes may partly be due to the fact that data provided on composite dishes for these countries had been less disaggregated to ingredient level compared to other countries, and that UK intakes calculated over three years were compared with published results of the first two years of data collection.

Comparisons were not undertaken for the other surveys, as there were no published niacin intake estimates for the Italian (Sette et al., 2011) or Dutch (van Rossum et al., 2011) surveys, as French published intakes were for preformed niacin (Afssa, 2009), as published intakes for Finnish adolescents (Hoppu et al., 2010) were for two days only (contrary to the EFSA dataset, see Appendix B), as published intakes for Finnish children (Kyttälä et al., 2010) included supplement consumption (contrary to the EFSA dataset), and as no matching publication was available for the Latvian survey.

Table 1: EFSA's average daily total niacin intake estimates, expressed as percentages of intakes reported in the literature

Country	% of published intakes (% range over different age classes in a specific survey)
Finland	105-109 % (FINDIET2012)
Germany	76-81 % (VELS, infants), 95-103 % (VELS, other age groups), 110-115 % (EsKiMo)
Ireland	105-111 % (NANS)
Sweden	114-121 % (Riksmaten)
UK	82 – 97 % (NDNS-Rolling Programme, Years 1-3)

Uncertainties in the estimates may be caused by inaccuracies in mapping food consumption data according to the FoodEx2 classification, in analysing or estimating niacin composition due to the use of borrowed values in the food composition database, and in replacing missing niacin values by values of similar foods or food groups. These inaccuracies may, in principle, cause both too high and too low estimates of total niacin intake. Overestimated values may also be related to differences in dealing with vitamin losses that might occur in processed foods. In this assessment on niacin, losses were based on the data for processed foods provided in the EFSA Food Composition Database project (Roe et al., 2013).

4. Overview of Dietary Reference Values and recommendations

4.1. Adults

The Nordic countries (Nordic Council of Ministers, 2014) set an AR at 1.3 mg NE/MJ based on studies in which niacin status was assessed using urinary excretion of niacin metabolites (SCF, 1993; Powers, 1999). The Recommended Intake (RI) was set at 1.6 mg NE/MJ. This would correspond to an intake of about 13-15 mg NE/day for women and 15-19 mg NE/day for men. However, it was stated that, when planning diets, niacin intake should not be lower than 13 mg NE/day when a low energy diet (< 8 MJ/day) is consumed. A lower intake level was set at 1 mg NE/MJ, thus 9 mg NE/day for women and 12 mg NE/day for men. At energy intakes below 8 MJ/day, the lower limit was estimated to be 8 mg NE/day.

The German-speaking countries (D-A-CH, 2013) followed a proposal by FAO/WHO (1978) to set niacin reference values in relation to energy intake as 1.6 mg NE/MJ and considered that niacin intake should not be below 13 mg NE/day in case of low energy requirement. Recommended intakes were calculated taking into account the guiding values for energy intake.

WHO/FAO (2004) based their reference values on two studies (Patterson et al., 1980; Shibata and Matsuo, 1989), along with earlier data from the 1950s, considering 12.5 mg NE/day, which corresponds to 5.6 mg NE/4 184 kJ (5.6 mg NE/1 000 kcal or about 1.3 mg NE/MJ), as being minimally sufficient for niacin intake in adults.

Afssa (2001) set a PRI of 6.0 mg NE/5 MJ (5.0 mg NE/1 000 kcal) derived from the minimum amount required to prevent pellagra and to restore normal excretion of NMN and 2-Pyr (Goldberger and Tanner, 1922; Goldsmith, 1956; Goldsmith et al., 1956; Horwitt et al., 1956; Jacob et al., 1989). Taking into account the mean energy intake for age and sex, reference values were set at 14 mg NE/day for men and 11 mg NE/day for women.

Based on three studies investigating the urinary excretion of NMN while on diets low or deficient in niacin (Goldsmith et al., 1955; Horwitt et al., 1956; Jacob et al., 1989), the Health Council of the Netherlands (2000) considered a urinary excretion of 1 mg/day of NMN to be the value below which niacin intake is inadequate. This value was judged to reflect an average intake of 11.6 mg NE/day at a normal protein intake (Goldsmith et al., 1952; Goldsmith et al., 1955; Horwitt et al., 1956; Jacob et al., 1989). It was concluded that there was no proven difference in the metabolism of niacin, but differences in energy intake between men (11.2 MJ/day) and women (8.5 MJ/day) were recognised (Hulshof et al., 1998). Therefore, an AR was set at 12 and 9 mg NE/day for men and women, respectively. A PRI of 17 mg NE/day for men and 13 mg NE/day for women aged 19 years or more was set.

IOM (1998) considered urinary NMN excretion to be the best marker for setting the Estimated Average Requirement (EAR). Based on four experimental studies (Goldsmith et al., 1952; Goldsmith et al., 1955; Horwitt et al., 1956; Jacob et al., 1989), an interpolated urinary NMN excretion of 1 mg/day was considered to reflect a niacin intake that is above the intake resulting in deficiency, and

a corresponding NE intake was calculated assuming a linear relationship between NMN excretion and niacin intake. The average (± SD) intake equivalent to the excretion of 1 mg NMN/day was calculated to be 11.6 ± 3.9 mg NE. The EAR was set at 12 mg NE/day for men and, with a small (approximately 10 %) decrease for the lower energy intake of women, at 11 mg NE/day for women. For the Recommended Dietary Allowance (RDA), a coefficient of variation (CV) of 15 % was used, as the data from the four experimental studies suggested a wider variation than 10 %, resulting in an RDA of 16 and 14 mg NE/day for men and women, respectively.

SCF (1993) based the AR of 1.3 mg NE/MJ on the results of depletion–repletion studies in which the amount of preformed niacin or tryptophan required to restore "normal" excretion of NMN and methyl pyridone carboxamide was determined (Horwitt et al., 1956; Kelsay, 1969).[11,12] Allowing for individual variation, the PRI was set at 1.6 mg NE/MJ, which was then expressed as mg NE/day based on the AR for energy derived by SCF (1993)[13]. SCF considered people on "low energy diets" and concluded that the requirement of subjects with usual intakes below 8 MJ/day may not be covered by the PRI of 1.6 mg NE/MJ and thus suggested a PRI of 13 mg NE/day for these subjects. The LTI was set at 1.0 mg NE/MJ.

The UK Committee on Medical Aspects of Food (COMA) (DH, 1991) based the AR of 5.5 mg NE/1 000 kcal (i.e. 1.3 mg NE/MJ) on the requirement for niacin to prevent or cure pellagra, or to normalise urinary excretion of NMN and of methyl pyridine carboxamide, in subjects maintained on niacin-deficient diets and in energy balance (Horwitt et al., 1956). Applying a CV of 10 %, a PRI of 6.6 mg NE/1 000 kcal (i.e. 1.6 mg NE/MJ) and a Lower Reference Nutrient Intake of 4.4 mg NE/1 000 kcal (i.e. about 1 mg NE/MJ) were derived.

An overview of DRVs for niacin for adults is presented in Table 2.

[11] The narrative review by Kelsay (1969) reported that an excretion of 0.5 mg NMN/g creatinine was found in subjects with daily intakes of about 5 mg niacin and 200 mg tryptophan (a total of 8.3 mg NE) when subjects began to show clinical evidence of pellagra (Interdepartmental Committee on Nutrition for National Defense, 1963. Manual for Nutrition Surveys, 249 pp.).

[12] Although they are not referenced in the SCF report on niacin, it is assumed in this Opinion that the data of Goldsmith (1952, 1955) were used in setting the AR and PRI.

[13] In its opinion on energy intakes for the European Community, SCF (1993) indicated that, when an average energy intake was used for converting reference values for nutrients expressed in µg or mg/MJ to values in mg/day, a value of 11.3 MJ/day for adult men and of 8.5 MJ/day for adult women were used, which were the mean for men and for women of the energy requirements calculated for four age classes (considering resting energy expenditure based on available observed body weights but without considering desirable physical activity).

Table 2: Overview of Dietary Reference Values for niacin for adults

	NNR 2012 [a]	D-A-CH (2013) [a]	WHO/FAO (2004) [b]	Afssa (2001) [c]	NL (2000)	IOM (1998)	SCF (1993)	DH (1991)
Age (years)	18-30	19-< 25	≥ 19	≥ 20	≥ 19	≥ 19	≥ 18	≥ 19
PRI Men (mg NE/day)	19	17	16	14	17	16	1.6 [d]	1.6 [d]
PRI Women (mg NE/day)	15	13	14	11	13	14	1.6 [d]	1.6 [d]
Age (years)	31-60	25-< 51						
PRI Men (mg NE/day)	18	16						
PRI Women (mg NE/day)	14	13						
Age (years)	61-74	51-< 65						
PRI Men (mg NE/day)	16	15						
PRI Women (mg NE/day)	13	13						
Age (years)	≥ 75	≥ 65						
PRI Men (mg NE/day)	15	13						
PRI Women (mg NE/day)	13	13						

(a): PRI of 1.6 mg NE/MJ (Nordic Council of Ministers, 2014).
(b): from a "minimally sufficient" amount of 1.3 mg NE/MJ.
(c): PRI of 1.2 mg NE/MJ.
(d): Expressed as mg NE/MJ.
NE: niacin equivalent (1 mg niacin = 1 niacin equivalent = 60 mg dietary tryptophan).
NL: Health Council of the Netherlands (2000).

4.2. Infants and children

The Nordic countries (Nordic Council of Ministers, 2014) used the adult RI of 1.6 mg NE/MJ to set RIs for infants and children over six months of age, adjusted for the reference energy intake values for children.

The German-speaking countries (D-A-CH, 2013) followed the proposal by FAO/WHO (1978) to set niacin DRVs in relation to energy intake as 1.6 mg/MJ for the derivation of recommended intakes for infants older than four months and children.

For infants aged 7-12 months, WHO/FAO (2004) calculated the requirement based on a niacin concentration of human milk of 1.5 mg/L and a tryptophan concentration of 210 mg/L (American Academy of Pediatrics Committee on Nutrition, 1985). Therefore, it was calculated that the total content of NE is approximately 5 mg/L or 4 mg NE/0.75 L of human milk consumed daily. PRIs for children were set, but no information was given on how the PRIs were derived.

For infants from birth to 12 months, Afssa (2001) recommended a daily intake of about 3 mg NE based on the average concentration of niacin and tryptophan in breast milk and a mean milk intake of 0.75 L/day. No data were found on which to base niacin requirements for children; therefore, requirements were adjusted from the adult values of 5 mg NE/1 000 kcal, considering the average energy requirements of children. The values derived for adolescents were the same as for adults.

The Health Council of the Netherlands (2000) set an Adequate Intake (AI) of 2 mg/day of niacin for infants from birth to five months based on an average concentration of niacin in breast milk of 2.1 mg/L (Fomon and McCormick, 1993). It was proposed that, as infants require tryptophan for protein metabolism, only preformed niacin would be considered in the derivation of the AI. For infants and children older than six months, no data were identified; therefore, the AI was calculated

by linear extrapolation between the AI of infants from birth to five months and the value of adults. An AI of 2 mg NE/day for infants aged 6-11 months was set.

For infants between birth and six months, IOM (1998) derived an AI for niacin based on the estimated niacin concentration of breast milk of 1.8 mg/L (Ford et al., 1983) and the reported mean intake of breast milk for this age group of 0.78 L/day (Hofvander et al., 1982; Butte et al., 1984; Chandra, 1984; Allen et al., 1991). Because of the high rate of protein turnover and the net positive nitrogen retention in infancy, tryptophan intake was not considered. Therefore, an AI was set at 2 mg/day of preformed niacin, after rounding up. For infants aged 7-12 months, an AI (in mg NE/day) was extrapolated from estimates of adult requirement by allometric scaling, using body weight to the power of 0.75 (and rounding). For children and adolescents, no data were found on which to base an EAR; therefore, EARs and RDAs were extrapolated from adults by allometric scaling.

For infants and children, SCF (1993) and UK COMA (DH, 1991) considered that there was no evidence that the requirement was different from that of adults, other than on the basis of average energy expenditure.

An overview of DRVs for niacin for children is presented in Table 3.

Table 3: Overview of Dietary Reference Values for niacin for children

	NNR 2012[(a)]	**D-A-CH (2013)**	**WHO (2004)**	**Afssa (2001)**	**NL (2000)**	**IOM (1998)**	**SCF (1993)**	**DH (1991)**
Age (months)	6-11	4-< 12	7-12	infants	6-11	7-12	6-11	7-12
PRI (mg NE/day)	5	5	4 [(b)]	3 [(b)]	2 [(b)]	4 [(b)]	1.6 [(c)]	1.6 [(c)]
Age (years)	1-< 2	1-< 4	1-3	1-3	1-3	1-3	1-17	1-18
PRI (mg NE/day)	7	7	6	6	4 [(b)]	6	1.6 [(c)]	1.6 [(c)]
Age (years)	2-5	4-< 7	4-6	4-6	4-8	4-8		
PRI (mg NE/day)	9	10	8	8	7 [(b)]	8		
Age (years)	6-9	7-< 10	7-9	7-9	9-13	9-13		
PRI (mg NE/day)	12	12	12	9	11 [(b)]	12		
Age (years)	10-13	10-< 13	10-18	10-12	14-18	14-18		
PRI Boys (mg NE/day)	15	15	16	10	17 [(b)]	16		
PRI Girls (mg NE/day)	14	13	16	10	13 [(b)]	14		
Age (years)	14-17	13-< 15		13-15				
PRI Boys (mg NE/day)	19	18		13				
PRI Girls (mg NE/day)	16	15		11				
Age (years)		15-< 19		16-19				
PRI Boys (mg NE/day)		17		14				
PRI Girls (mg NE/day)		13		11				

(a): Nordic Council of Ministers (2014).
(b): AI.
(c): Expressed as mg NE/MJ.
NE: niacin equivalent. NL: Health Council of the Netherlands (2000).

4.3. Pregnancy and lactation

The Nordic countries (Nordic Council of Ministers, 2014) recommended an additional 1 mg NE/day (girls aged 14-17 years) to 3 mg NE/day (women of 31 years and older) for pregnant women, based on the increased energy requirement, and thus set an RI of 17 mg/day for pregnancy. They recommended an extra intake of 4 mg NE/day (girls aged 14-17 years) to 6 mg NE/day (women of 31 years and older), based on the niacin content of breast milk and the increased energy requirement, and thus set an RI of 20 mg/day for lactation.

The German-speaking countries (D-A-CH, 2013) acknowledged that the formation of niacin from tryptophan is increased during pregnancy. Nevertheless, and taking into account the increased energy requirement in pregnancy, an additional intake of 2 mg NE/day was recommended; thus a PRI of 15 mg/day for pregnancy was set. The German-speaking countries assumed that 1.3 mg preformed niacin and 2.8 mg NE from tryptophan are secreted with 0.75 L of milk per day. Therefore, an additional intake of 4 mg NE/day was recommended for lactating women; thus the PRI was set at 17 mg/day.

Considering the energy requirement for non-pregnant women and that of the entire pregnancy, WHO/FAO (2004) calculated that the niacin requirement above that of non-pregnant women was 308 mg NE (5.6 mg NE/4 184 kJ) for the entire pregnancy or 1.7 mg NE/day for the second and third trimesters. In addition, about 2 mg NE/day was assumed to be required for growth in maternal and fetal compartments (IOM, 1998). Thus, the PRI was set at 18 mg/day for pregnancy. WHO/FAO (2004) estimated that 1.4 mg preformed niacin is secreted daily with breast milk, and that an additional amount of less than 1 mg is required to support the energy expenditure of lactation. Hence, it was assumed that lactating women require an additional 2.4 mg NE/day. Thus, the PRI was set at 17 mg/day.

For pregnant women, Afssa (2001) advised an increase of 5 mg NE/day to meet the increased energy needs of pregnancy, setting a PRI of 16 mg NE/day. Afssa also advised an increase of 4 mg NE/day to cover the amount secreted with milk, proposing a PRI of 15 mg NE/day for lactating women.

The Health Council of the Netherlands (2000) based its reference values on increased energy consumption (equivalent to 1 mg NE/day) and the growth of tissue in the mother and fetal compartments (2 mg NE/day). Using the factorial method, an AR of 12 mg NE/day and a PRI of 17 mg NE/day were set. The Health Council of the Netherlands (2000) set an AR of 14 mg NE/day for lactating women based on the average daily loss of 2 mg/day of niacin in breast milk and increased energy needs for milk production equivalent to 3 mg NE/day, which were added to the AR for non-lactating women. A PRI of 20 mg NE/day was set for lactating women.

IOM (1998) found no direct evidence to suggest a change in niacin requirement during pregnancy but estimated an increase of 3 mg NE/day (added to the EAR of non-pregnant women) to cover increased energy utilisation and growth of maternal and fetal compartments, especially during the second and third trimesters; thus, using a CV of 15 %, an RDA of 18 mg NE/day was set. IOM estimated that 1.4 mg of preformed niacin is secreted daily during lactation. Therefore, along with an amount of 1 mg to cover the energy expenditure of milk production, an additional 2.4 mg NE/day was recommended for women exclusively breastfeeding, added to the EAR for non-lactating women and rounded down, to result in an RDA of 17 mg/day.

SCF (1993) concluded that there was no need for an increased niacin intake in pregnancy as the hormonal changes associated with pregnancy increased the efficiency of synthesis of nicotinamide nucleotides from tryptophan. SCF considered an increase in intake of 2 mg NE/day to allow for the niacin secreted in milk.

UK COMA (DH, 1991) concluded that it was unnecessary to increase niacin intake during pregnancy as the additional requirement would be met by changes in the metabolism of tryptophan (Wertz et al., 1958). Based on a preformed niacin concentration of 2.7 mg/L in mature human milk, UK COMA recommended an increment of 2.3 mg NE/day in addition to the PRI for non-pregnant women.

An overview of DRVs for niacin for pregnant and lactating women is presented in Table 4.

Table 4: Overview of Dietary Reference Values for niacin for pregnant women

	NNR 2012 [(a)]	D-A-CH (2013)	WHO/FAO (2004)	Afssa (2001)	NL (2000) [(b)]	IOM (1998) [(c)]	SCF (1993)	DH (1991)
PRI for pregnancy (mg NE/day)	17	15 [(d)]	18	16	17	18	1.6 [(e)]	1.6 [(e)]
PRI for lactation (mg NE/day)	20	17	17	15	20	17	+ 2	+ 2.3

(a): Nordic Council of Ministers (2014).
(b): Taken from the original Dutch table, not the English summary.
(c): Age 14-50 years.
(d): From four months.
(e): Expressed as mg NE/MJ.
NE: niacin equivalent.
NL: Health Council of the Netherlands (2000).

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

5.1. Indicators of niacin requirement

5.1.1. Adults

5.1.1.1. Pellagra

In a depletion–repletion study on seven healthy men (23-39 years, n = 12 included, five drop-outs) (Jacob et al., 1989), all subjects received an initial diet containing about 10.5 MJ/day and 19.6 mg NE/day for 13 days (1.9 mg NE/MJ or 7.8 mg NE/1 000 kcal), then consumed one of two "low" NE diets, either 6.1 mg NE/day (0.58 mg NE/MJ or 2.44 mg NE/1 000 kcal) or 10.1 mg NE/day (about 0.97 mg NE/MJ or 4 mg NE/1 000 kcal) for 35 days. Energy intakes were individually adjusted for maintenance of body weight. No signs of pellagra were observed in these subjects.

Goldsmith et al. (1952) carried out a study in seven women with psychoneurosis (aged 25-54 years), who consumed either a "corn" diet[14], which provided daily 4.7 mg niacin, 190 mg tryptophan and 8.4 MJ, thus about 0.94 mg NE/MJ (3.9 mg NE/1 000 kcal), or a "wheat" diet, which provided daily 5.7 mg niacin, 230 mg tryptophan and 7.9 MJ, thus about 1.2 mg NE/MJ (5 mg NE/1 000 kcal). The energy content of the diets was adjusted to meet the subjects' energy requirements. In the first phase of the experiment on three subjects, no signs of pellagra were observed either on the corn diet (n = 2) for 40 and 42 days or on the wheat diet (n = 1) for 95 days. Three other subjects then followed the corn diet for 81, 135 and 111 days and all developed pellagra between 50 and 60 days, whereas a fourth subject who received the corn diet supplemented with 2 mg/day of nicotinamide for 122 days (i.e. about 1.2 mg NE/MJ or 5 mg NE/1 000 kcal) did not develop pellagra.

Goldsmith et al. (1955) studied nine women and one man (aged 26-60 years, some of whom were psychiatric or neurology patients) who were given experimental diets for up to 135 days. The diets contained approximately 4.7 mg niacin and 190 mg tryptophan ("corn" diet) or approximately 5 mg

[14] i.e. "maize" in UK English.

niacin and 200 mg tryptophan ("wheat" diet) and about 8.4 MJ; thus, both diets provided 0.94-0.99 mg NE/MJ (3.9-4.1 mg NE/1 000 kcal) per day. The energy content of the diets was adjusted to meet the subjects' energy requirements. Three subjects followed the "wheat" diet for 95 to 105 days, six followed the "corn diet" supplemented with nicotinamide to achieve total niacin intakes of 4.6 to 21.2 mg/day (each supplement administered for a period of 12 to 20 days and each subject studied at four to six levels of niacin intake) and one followed both (unsupplemented) diets alternating every 20 days for 80 days in total. One out of the three subjects on the wheat diet (0.99 mg NE/MJ or 4.1 mg NE/1 000 kcal) developed pellagra after 80 days and so did the subject on unsupplemented alternating diets.

Horwitt et al. (1956) studied 40 male psychiatric patients (aged ≥ 30 years except for one subject) divided into five groups: one group (n = 9) consuming a general hospital diet (HD) *ad libitum* supplemented with 10 mg/day nicotinamide three times a week and four groups in which the subjects consumed, according to "appetite, size and personal preference", 90 to 120 % of a basal diet containing 5.8 mg niacin and 265 mg tryptophan for 9.6 MJ, thus about 1.06 mg NE/MJ (4.5 mg NE/1 000 kcal). Among these four groups, two groups were supplemented with 2 mg/day riboflavin and either 10 mg/day nicotinamide (n = 7, i.e. about 2.1 mg NE/MJ) or tryptophan (n = 8, 50 mg/day for 10 weeks, i.e. about 1.15 mg NE/MJ, 100 mg/day afterwards, i.e. about 1.24 mg NE/MJ). The original design of the study was respected for the first 37 weeks only. No signs of pellagra were observed in these patients. Horwitt et al. (1956) also compared their data on niacin and tryptophan requirements (n = 15 subjects, followed up to 87 weeks) with those (n = 20) from two other similar publications (Frazier and Friedemann, 1946; Goldsmith et al., 1952) and an unpublished source. The authors reported that this comparison showed that no signs of pellagra were observed in subjects consuming about 8.4-11.5 MJ and 9.2-12.3 mg NE, thus with an intake of about 1 mg NE/MJ (4.4 mg NE/1 000 kcal). Horwitt et al. also reported, based on this comparison, that signs of pellagra were observed in some subjects (from the other three data sources considered) consuming less than 8.8 MJ and 7.4-8.2 mg NE or about 12.5 MJ and 12.2 mg NE, thus at an intake of about 0.9-1 mg NE/MJ (3.7-4.1 mg NE/1 000 kcal), assuming an energy intake of 2 000 kcal for this calculation. It was therefore considered that diets providing less than about 8.4 MJ (2 000 kcal) should provide at least 8.8 mg NE (Horwitt et al., 1956; Goldsmith, 1958).

The Panel notes that, in these studies performed on heterogeneous groups of subjects, mostly patients for whom no alteration in energy metabolism and niacin requirements is assumed, symptoms of pellagra developed in subjects consuming less than about 1 mg NE/MJ for more than 50 days. The Panel also notes that, on the basis of its biochemical role and of the results of these studies, niacin requirement depends on energy intake, that intakes of about 1-1.2 mg NE/MJ (4.4-5 mg NE/1 000 kcal) prevented the development of pellagra and that this relationship was established for diets that were designed to maintain subjects' body weight.

5.1.1.2. Urinary niacin metabolites

The Panel considers urinary excretion of niacin metabolites, NMN and 2-Pyr, as a suitable criterion for deriving the requirement for niacin and that the other markers of niacin intake/status cannot be used as criteria for deriving DRVs for niacin (see Section 2.3.).

In the depletion–repletion study of Jacob et al. (1989), a "low" intake of 6.1 or 10.1 mg NE/day, i.e. below 1 mg NE/MJ, for 35 days resulted in a significant fall in urinary NMN excretion (0.80 ± 0.13 mg/day and 0.81 ± 0.14 mg/day, respectively) and 2-Pyr excretion (1.00 ± 0.05 mg/day and 3.10 ± 0.71 mg/day, respectively) compared with the excretion of these metabolites (respectively, 2.90 ± 0.41 and 7.21 ± 1.86 mg/day) on the initial diet (19.6 mg NE/day, about 1.9 mg NE/MJ), while no symptoms of pellagra were observed. After two weeks on a "repletion" diet containing 19.2 mg NE/day (1.8 mg NE/MJ or 7.68 mg NE/1 000 kcal), a significant increase in urinary NMN excretion (1.82 ± 0.08 mg/day) compared with the "low" diets was observed, while urinary 2-Pyr

excretion was 6.25 ± 0.40 mg/day and thus six-fold ($p < 0.05$) or two-fold ($p > 0.05$) higher compared with the intakes of 6.1 or 10.1 mg NE/day, respectively. Urinary 2-Pyr excretion over four hours after an oral dose of nicotinamide was significantly greater during the initial period of 19.6 mg NE/day compared with that at the end of the "depletion" period (intakes of 6.1 or 10.1 mg NE/day) and of the "repletion" period (intake of 19.2 mg NE/day). The authors stated that the latter difference may reflect an incomplete repletion of niacin body stores.

In the first phase of the experiment of Goldsmith et al. (1952), during which no signs of pellagra were observed, mean urinary NMN concentrations decreased in both subjects on the "corn" diet (0.9-1.2 mg/day during the last two weeks) and in the subject on the "wheat" diet (1.1 mg/day during the last 33 days), and urinary excretion of 2-Pyr decreased in all three subjects to undetectable concentrations after the first two weeks. In the second phase of this experiment, urinary NMN excretion decreased to 0.5-0.7 mg/day in all three subjects who developed pellagra on the "corn" diet (providing less than about 1 mg NE/MJ) and to 0.9 mg/day in the supplemented subject on the "corn" diet without pellagra (i.e. receiving about 1.2 mg NE/MJ), while urinary excretion of 2-Pyr decreased to undetectable concentrations in all four subjects.

In all three subjects on the "wheat" diet (providing less than about 1 mg NE/MJ) (Goldsmith et al., 1955), urinary NMN excretion decreased gradually around the 80th day down to 0.6-0.8 mg/day while 2-Pyr excretion decreased to concentrations of about 0.3-0.7 mg/day, but only one subject developed pellagra. In the subjects supplemented with nicotinamide to achieve total niacin intakes of 4.6 to 21.2 mg/day, the relationship between niacin intakes and urinary excretion of niacin metabolites was found to differ between niacin intakes up to about 8-10 mg/day and intakes above: about 0.2 mg/day of metabolites were excreted per each additional mg of niacin up to the intake of 8-10 mg/day above which the excretion significantly increased to 0.6 mg of metabolites per each additional mg of niacin intake.

The Panel notes that an intake of at least 8 mg niacin in addition to the tryptophan intake from the diet (about 200 mg), i.e. an intake of at least 11 mg NE/day, which corresponds to 1.3 mg NE/MJ (about 5.5 mg NE/1 000 kcal), was sufficient to prevent depletion and maintain niacin body stores as indicated by a sharp increase in urinary excretion of niacin metabolites above this intake. The Panel also notes that diets providing less than about 1 mg NE/MJ (about 4.4 mg NE/1 000 kcal) are insufficient to maintain niacin body stores as indicated by significantly lower urinary excretion of 2-Pyr after oral nicotinamide dose tests.

5.1.2. Conclusions on indicators of niacin requirement in adults

Based on the two papers by Goldsmith et al. (1952; 1955) using urinary excretion of niacin metabolites as an endpoint, an intake of 1.3 mg NE/MJ (about 5.5 mg NE/1 000 kcal) was sufficient to cover the requirement for niacin. The available data (Goldsmith et al., 1952; Goldsmith et al., 1955; Horwitt et al., 1956; Jacob et al., 1989) also show that intakes below about 1 mg NE/MJ (about 4.4 mg NE/1 000 kcal) are insufficient to maintain niacin body stores. No new pertinent data have been published since then.

The Panel concludes that there are no new data to amend the DRVs for niacin (expressed in mg NE/MJ) proposed by SCF in 1993.

5.1.3. Infants

The Panel is unaware of any data in infants aged 7-11 months on indicators of niacin requirement. There is no evidence that the relationship between niacin requirement and energy requirement in infants aged 7-11 months differs from that of adults.

5.1.4. Children

The Panel is unaware of any new data in children on indicators of niacin requirement published after the report by SCF (1993) which did not cite any specific data for this population group.

The Panel notes the lack of evidence on indicators of niacin requirement in children. There is no evidence that the relationship between niacin requirement and energy requirement in children differs from that of adults.

5.1.5. Pregnancy

The Panel is unaware of any data in pregnant women on indicators of niacin requirement. There is no evidence that the relationship between niacin requirement and energy requirement in pregnancy differs from that of non-pregnant women.

5.1.6. Lactation

The Panel is unaware of any data in lactating women on indicators of niacin requirement. There is no evidence that the relationship between niacin requirement and energy requirements in lactation differs from that of non-lactating women.

5.2. Niacin intake and health consequences

A comprehensive search of the literature published between January 1990 and January 2012 was performed as preparatory work to this assessment in order to identify new data on relevant health outcomes upon which DRVs for niacin may potentially be based (Eeuwijk et al., 2012).

No intervention studies are available on niacin intake and health outcomes. The relationship between niacin intakes and chronic disease outcomes has been investigated in observational (case–control, cross–sectional, prospective cohort) studies, where an association between niacin intake and disease outcomes might be confounded by uncertainties inherent in the methodology used for the assessment of niacin intakes and by the effect of other dietary, lifestyle or undefined factors on the health or disease outcomes investigated.

No association was found between niacin intake and all-cause mortality (Huang et al., 2012); breast, endometrial, ovarian, colorectal and lung cancer (Sellers et al., 2001; Shin et al., 2006; Kabat et al., 2008; Shrubsole et al., 2011); cognitive function (Morris et al., 2004; Woo et al., 2006); pneumonia (Neuman et al., 2007); ovulatory infertility and premenstrual syndrome (Chocano-Bedoya et al., 2011); and overactive bladder syndrome (Dallosso et al., 2004; Neuman et al., 2007; Chavarro et al., 2008; Chocano-Bedoya et al., 2011; Huang et al., 2012). Conflicting results were observed in relation to maternal niacin intake and infant birth weight (Weigel et al., 1991; Lagiou et al., 2005). Associations between niacin intake and prevalence of nuclear cataract (Cumming et al., 2000) and genome stability (Fenech et al., 2005) were reported; however, similar associations with a number of other nutrients were noted.

The Panel considers that the data available on niacin intake and health outcomes cannot be used for deriving DRVs for niacin.

6. Data on which to base Dietary Reference Values

The Panel notes that no new scientific data that would necessitate an amendment of the AR and PRI for niacin have become available since the publication of the SCF report in 1993. The Panel therefore endorses the relationship proposed by SCF (1993) between niacin requirement and energy

requirement. Niacin requirement is expressed in NE as the sum of preformed niacin plus that provided by endogenous synthesis from tryptophan, by energy unit. Taking into account the reference energy intake, i.e. the AR for energy, the intake of NE can be expressed as mg NE/day (Appendices G–J). The ARs for energy for various Physical Activity Levels (PAL values) can be found in the Scientific Opinion on Dietary Reference Values for energy (EFSA NDA Panel, 2013).

The Panel notes that, as for other nutrient reference values, DRVs for niacin are set under the assumption that intakes of other essential nutrients, particularly iron, riboflavin, vitamin B6 and protein, and energy are adequate.

6.1. Adults

In the absence of new scientific data, the Panel endorses the AR for adults (men and women) adopted by SCF (1993) and set at 1.3 mg NE/MJ. The Panel decides to apply the same CV of 10 % as SCF (1993) and also endorses the PRI of 1.6 mg NE/MJ (6.6 mg NE/1 000 kcal). The PRIs in mg NE/day are presented in Appendix G.

6.2. Infants

For infants aged 7-11 months, the Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement differs from that of adults. Therefore, for infants, the AR and PRI (expressed as mg NE/MJ) for adults are applied. The PRIs in mg NE/day are presented in Appendix H.

6.3. Children

The Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement in children and adolescents differs from that of adults. Therefore, for children and adolescents, the AR and PRI (expressed as mg NE/MJ) for adults are applied. The PRIs in mg NE/day are presented in Appendix I.

6.4. Pregnancy

The Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement in pregnancy differs from that of other adults. The Panel notes that the energy requirement in pregnant women is increased (by 0.29 MJ/day, 1.1 MJ/day and 2.1 MJ/day, for the first, second and third trimesters, respectively) (EFSA NDA Panel, 2013). The PRI in mg NE/day is increased proportionally compared with that in non-pregnant women (i.e. using the AR for niacin of 1.3 mg NE/MJ, the AR for additional energy for pregnancy or lactation and a CV of 10 %), as presented in Appendix J.

6.5. Lactation

The Panel considers that there is no evidence that the relationship between niacin requirement and energy requirement in lactating women differs from that of other adults. The Panel notes that the energy requirement in lactation is increased by 2.1 MJ/day (EFSA NDA Panel, 2013). The Panel considers that the additional niacin intake in proportion to this additional energy intake covers the amount of niacin secreted in breast milk; therefore no further compensation is considered necessary. The PRI in mg NE/day is increased compared with that in non-lactating women, as presented in Appendix J.

CONCLUSIONS

The Panel concludes that no new scientific data have become available to change the Population Reference Intake (PRI) for niacin set by SCF in 1993, and endorses the PRI at 1.6 mg NE/MJ for all population groups.

Table 5: Summary of Dietary Reference Values for niacin

Age	PRI (mg NE/MJ)
7 months to ≥ 18 years [(a)]	1.6

(a): including pregnancy and lactation.
NE: niacin equivalent (1 mg niacin = 1 niacin equivalent = 60 mg dietary tryptophan).

RECOMMENDATIONS FOR RESEARCH

Future studies should investigate indicators of niacin requirement in infants aged 7-11 months, children, and pregnant and lactating women.

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APPENDICES

Appendix A. Niacin content of human milk from healthy mothers

Reference	Number of women (*number of samples*)	Country	Stage of lactation	Niacin concentration (mg/L) mean	range	Form of niacin analysed
Ford et al. (1983) [(a)]	35 (total)	UK				Nicotinic acid
	7 (*18*)		1-5 days	0.50	0.30-0.91	
	8 (*22*)		6-15 days	1.42	0.26-3.00	
	23 (*24*)		16-244 days	1.82	1.20-2.80	
DHSS (1977) [(a)]	96	UK	14-63 days	2.3	-	Nicotinic acid

(a) Supplementation status for niacin unknown (not reported).

Appendix B. Dietary surveys from the EFSA Comprehensive Food Consumption Database included in the nutrient intake calculation for niacin

Country	Dietary survey (Year)	Year	Method	Days	Age (years)	Number of subjects [b]						
						Infants 6-11 months	Children 1-< 3 years	Children 3-< 10 years	Adolescents 10-< 18 years	Adults 18-< 65 years	Adults 65-< 75 years	Adults ≥ 75 years
Finland/1	DIPP	2000-2010	Dietary record	3	< 1-6	499	500	750				
Finland/2	NWSSP	2007-2008	48-hour dietary recall [a]	2x2 [a]	13-15				306			
Finland/3	FINDIET2012	2012	48-hour dietary recall [a]	2 [a]	25-74					1 295	413	
France	INCA2	2006-2007	Dietary record	7	3-79			482	973	2 276	264	84
Germany/1	EsKiMo	2006	Dietary record	3	6-11			835	393			
Germany/2	VELS	2001-2002	Dietary record	6	< 1-4	159	347	299				
Ireland	NANS	2008-2010	Dietary record	4	18-90					1 274	149	77
Italy	INRAN-SCAI 2005-06	2005-2006	Dietary record	3	< 1-98	16 [b]	36 [b]	193	247	2 313	290	228
Latvia	FC_PREGNANTWOMEN 2011	2011	24-hour dietary recall	2	15-45				12 [b]	991 [c]		
Netherlands	VCPBasis_AVL	2007-2009	24-hour dietary recall	2	7-69			447	1 142	2 057	173	
Sweden	RISKMATEN	2010-2011	Dietary records (Web) [d]	4	18-80					1 430	295	72
United Kingdom	NDNS - Rolling Programme (Years 1-3)	2008-2011	Dietary record	4	1-94		185	651	666	1 266	166	139

(a): A 48-hour dietary recall comprising two consecutive days.
(b): 5th or 95th percentile intakes calculated over a number of subjects lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and therefore for these dietary surveys/age classes the 5th and 95th percentile estimates will not be presented in the intake results.
(c): One subject was excluded from the dataset due to only one 24-hour dietary recall day being available, i.e. the final n = 990.
(d): The Swedish dietary records were introduced through the Internet.

Appendix C. Total niacin intakes among males in different surveys according to age classes and country (NE, mg/day and mg/MJ)

Age class	Country	Survey	Intakes expressed in mg NE/day					Intakes expressed in mg NE/MJ				
			N	Average	Median	P5	P95	N	Average	Median	P5	P95
Infants	Finland	DIPP_2001_2009	247	10.9	9.8	0.9	24.3	245	3.5	3.4	2.3	5.3
	Germany	VELS	84	8.7	8.2	4.7	14.2	84	2.6	2.7	1.6	3.5
	Italy	INRAN_SCAI_2005_06	9	7.2	6.9	(a)	(a)	9	2.1	2.2	(a)	(a)
Boys 1-< 3 years	Finland	DIPP_2001_2009	245	18.9	17.5	9.5	33.6	245	3.9	3.9	2.9	5.3
	Germany	VELS	174	12.9	12.1	7.7	20.5	174	2.7	2.7	1.9	3.7
	Italy	INRAN_SCAI_2005_06	20	20.1	20.1	(a)	(a)	20	3.9	4.0	(a)	(a)
	United Kingdom	NDNS-Rolling Programme Years 1-3	107	18.1	17.6	11.5	25.8	107	3.7	3.7	2.7	4.9
Boys 3-< 10 years	Finland	DIPP_2001_2009	381	23.3	22.5	14.7	34.7	381	3.9	3.8	2.9	5.1
	France	INCA2	239	30.4	29.0	16.6	50.1	239	4.8	4.7	3.5	6.4
	Germany	EsKiMo	426	25.0	24.4	16.5	35.1	426	3.3	3.2	2.4	4.4
	Germany	VELS	146	15.9	16.1	10.5	22.5	146	2.8	2.8	2.1	3.7
	Italy	INRAN_SCAI_2005_06	94	31.5	29.5	17.7	49.4	94	4.3	4.3	2.9	6.3
	Netherlands	VCPBasis_AVL2007_2009	231	25.5	24.5	15.0	38.6	231	3.0	2.9	1.9	4.3
	United Kingdom	NDNS-Rolling Programme Years 1-3	326	23.4	22.8	13.4	34.6	326	3.8	3.7	2.6	5.4
Boys 10-< 18 years	Finland	NWSSP07_08	136	33.3	32.5	19.3	49.0	136	4.1	4.0	2.9	5.6
	France	INCA2	449	41.0	38.5	25.0	66.3	449	5.2	5.0	3.7	7.1
	Germany	EsKiMo	197	27.1	25.7	17.2	42.8	197	3.4	3.3	2.3	4.6
	Italy	INRAN_SCAI_2005_06	108	41.4	40.4	24.7	64.5	108	4.3	4.3	3.2	5.4
	Netherlands	VCPBasis_AVL2007_2009	566	35.5	33.0	19.9	59.5	566	3.3	3.2	2.1	5.2
	United Kingdom	NDNS-Rolling Programme Years 1-3	340	31.6	30.5	18.2	47.9	340	4.0	3.9	2.6	5.9
Men 18-< 65 years	Finland	FINDIET2012	585	42.6	41.3	22.4	68.9	585	4.7	4.5	2.9	6.9
	France	INCA2	936	47.3	45.8	27.2	73.6	936	5.4	5.3	3.8	7.7
	Ireland	NANS_2012	634	53.4	52.0	31.3	77.3	634	5.4	5.2	3.8	7.5
	Italy	INRAN_SCAI_2005_06	1 068	42.2	40.9	25.7	63.1	1 068	4.8	4.7	3.5	6.7
	Netherlands	VCPBasis_AVL2007_2009	1 023	46.6	43.9	26.6	76.0	1 023	4.2	4.0	2.7	6.1
	Sweden	Riksmaten 2010	623	50.1	48.4	26.7	78.2	623	5.1	5.0	3.6	7.4

Age class	Country	Survey	Intakes expressed in mg NE/day					Intakes expressed in mg NE/MJ				
			N	Average	Median	P5	P95	N	Average	Median	P5	P95
	United Kingdom	NDNS-Rolling Programme Years 1-3	560	40.1	38.0	20.5	63.0	560	4.7	4.6	2.8	6.8
Men 65-< 75 years	Finland	FINDIET2012	210	35.7	35.1	19.7	56.8	210	4.5	4.4	2.6	6.7
	France	INCA2	111	45.5	44.7	23.1	72.8	111	5.3	5.1	3.9	7.3
	Ireland	NANS_2012	72	44.8	44.1	23.8	69.1	72	5.2	5.0	3.4	7.5
	Italy	INRAN_SCAI_2005_06	133	41.5	41.5	22.7	61.9	133	5.1	5.0	3.7	7.0
	Netherlands	VCPBasis_AVL2007_2009	91	39.6	38.1	23.2	57.9	91	4.4	4.1	2.7	7.0
	Sweden	Riksmaten 2010	127	44.5	41.7	28.2	69.6	127	5.2	5.0	3.5	7.0
	United Kingdom	NDNS-Rolling Programme Years 1-3	75	37.9	37.5	11.7	56.1	75	4.6	4.5	2.5	6.6
Men ≥ 75 years	France	INCA2	40	40.2	38.4	(a)	(a)	40	5.2	5.1	(a)	(a)
	Ireland	NANS_2012	34	40.2	41.2	(a)	(a)	34	5.4	5.3	(a)	(a)
	Italy	INRAN_SCAI_2005_06	69	39.2	36.8	24.5	56.4	69	4.8	4.8	3.5	6.9
	Sweden	Riksmaten 2010	42	40.3	39.3	(a)	(a)	42	4.8	4.8	(a)	(a)
	United Kingdom	NDNS-Rolling Programme Years 1-3	56	31.6	29.6	(a)	(a)	56	4.6	4.5	(a)	(a)

(a): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and therefore for these dietary surveys/age classes the 5^{th} and 95^{th} percentile estimates will not be presented in the intake results.

Appendix D. Total niacin intakes among females in different surveys according to age classes and country (NE, mg/day and mg/MJ)

Age class	Country	Survey	Intakes expressed in mg NE/day					Intakes expressed in mg NE/MJ				
			N	Average	Median	P5	P95	N	Average	Median	P5	P95
Infants	Finland	DIPP_2001_2009	252	10.2	9.3	0.8	22.6	251	3.5	3.4	2.0	5.1
	Germany	VELS	75	7.6	7.5	4.3	12.0	75	2.5	2.5	1.6	3.4
	Italy	INRAN_SCAI_2005_06	7	8.2	7.2	(a)	(a)	7	2.7	2.4	(a)	(a)
Girls 1-< 3 years	Finland	DIPP_2001_2009	255	17.7	16.5	7.4	29.5	255	4.0	3.9	2.8	5.6
	Germany	VELS	174	11.9	11.7	6.9	17.9	174	2.8	2.7	1.9	3.9
	Italy	INRAN_SCAI_2005_06	16	17.8	16.3	(a)	(a)	16	3.6	3.8	(a)	(a)
	United Kingdom	NDNS-Rolling Programme Years 1-3	78	16.9	17.0	10.7	22.9	78	3.8	3.6	2.6	5.4
Girls 3-< 10 years	Finland	DIPP_2001_2009	369	20.5	20.3	12.9	29.6	369	3.8	3.8	2.9	5.0
	France	INCA2	243	26.4	25.7	16.7	40.3	243	4.7	4.6	3.5	6.3
	Germany	EsKiMo	409	22.6	22.1	14.2	34.2	409	3.3	3.2	2.4	4.5
	Germany	VELS	147	14.3	13.9	9.3	21.0	147	2.8	2.7	1.9	3.8
	Italy	INRAN_SCAI_2005_06	99	29.9	29.7	17.7	42.5	99	4.2	4.1	3.2	5.6
	Netherlands	VCPBasis_AVL2007_2009	216	24.2	23.0	14.6	36.4	216	3.0	2.9	1.9	4.3
	United Kingdom	NDNS-Rolling Programme Years 1-3	325	21.6	21.6	12.6	31.5	325	3.7	3.7	2.5	5.2
Girls 10-< 18 years	Finland	NWSSP07_08	170	25.4	24.7	15.1	36.6	170	3.9	3.9	2.9	5.0
	France	INCA2	524	31.7	30.7	17.5	49.3	524	5.0	4.8	3.6	7.0
	Germany	EsKiMo	196	24.9	24.7	16.0	35.2	196	3.4	3.2	2.5	4.8
	Italy	INRAN_SCAI_2005_06	139	33.2	32.3	20.1	48.2	139	4.2	4.1	3.2	5.4
	Latvia [b]	FC_PREGNANTWOMEN_2011	12	38.1	36.4	(a)	(a)	12	3.8	3.9	(a)	(a)
	Netherlands	VCPBasis_AVL2007_2009	576	28.3	27.3	16.0	43.4	576	3.2	3.1	2.1	4.7
	United Kingdom	NDNS-Rolling ProgrammeYears 1-3	326	25.9	25.1	14.4	40.6	326	3.9	3.7	2.5	5.6
Women 18-< 65 years	Finland	FINDIET2012	710	31.1	29.6	18.3	46.6	710	4.4	4.2	2.8	6.8
	France	INCA2	1 340	34.2	33.2	18.9	53.5	1 340	5.3	5.1	3.7	7.6
	Ireland	NANS_2012	640	35.4	35.0	21.0	53.0	640	4.9	4.7	3.4	6.8

Age class	Country	Survey	Intakes expressed in mg NE/day					Intakes expressed in mg NE/MJ				
			N	Average	Median	P5	P95	N	Average	Median	P5	P95
	Italy	INRAN_SCAI_2005_06	1 245	35.1	34.0	20.8	50.0	1 245	4.8	4.7	3.4	6.6
	Latvia [(b)]	FC_PREGNANTWOMEN_2011	990	39.0	37.1	22.1	62.3	990	4.6	4.4	2.8	7.4
	Netherlands	VCPBasis_AVL2007_2009	1 034	33.0	32.0	18.4	50.9	1 034	4.0	3.8	2.5	6.0
	Sweden	Riksmaten 2010	807	36.7	35.3	20.8	55.5	807	4.9	4.7	3.3	7.0
	United Kingdom	NDNS-Rolling Programme Years 1-3	706	29.5	29.0	15.1	45.9	706	4.6	4.4	2.8	6.8
Women 65-< 75 years	Finland	FINDIET2012	203	27.4	26.0	15.0	42.9	203	4.5	4.3	2.9	6.7
	France	INCA2	153	32.6	32.0	18.3	50.6	153	5.2	5.2	3.8	7.1
	Ireland	NANS_2012	77	34.6	35.4	21.1	46.8	77	5.2	5.0	3.9	7.0
	Italy	INRAN_SCAI_2005_06	157	33.6	33.4	17.9	49.0	157	5.1	4.8	3.6	7.1
	Netherlands	VCPBasis_AVL2007_2009	82	30.7	28.9	17.8	45.3	82	4.2	4.1	2.8	5.9
	Sweden	Riksmaten 2010	168	35.5	34.0	21.0	55.2	168	5.1	4.9	3.8	6.8
	United Kingdom	NDNS-RollingProgramme Years 1-3	91	30.0	29.3	19.2	41.6	91	5.1	5.1	3.5	7.1
Women ≥ 75 years	France	INCA2	44	30.6	30.1	[(a)]	[(a)]	44	5.1	5.2	[(a)]	[(a)]
	Ireland	NANS_2012	43	32.5	30.3	[(a)]	[(a)]	43	5.2	5.1	[(a)]	[(a)]
	Italy	INRAN_SCAI_2005_06	159	32.0	31.6	18.7	45.8	159	4.8	4.7	3.5	6.6
	Sweden	Riksmaten 2010	30	35.4	35.6	[(a)]	[(a)]	30	5.1	4.8	a	a
	United Kingdom	NDNS-Rolling Programme Years 1-3	83	27.8	27.0	17.4	37.3	83	4.7	4.6	3.0	6.5

(a): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011b) and therefore for these dietary surveys/age classes the 5^{th} and 95^{th} percentile estimates will not be presented in the intake results.

(b): Pregnant women only.

Appendix E. Minimum and maximum percentage contribution of different FoodEx2 level1 food groups to niacin intakes among males

Food groups	Infants	Children 1-< 3 years	Children 3-< 10 years	Adolescents 10-< 18 years	Adults 18-< 65 years	Adults 65-< 75 years	Adults ≥ 75 years
Additives, flavours, baking and processing aids	< 0.1	< 0.1 - 0.2	0 - 0.8	0 - 1.3	0 - 0.2	0	0
Alcoholic beverages	< 0.1	< 0.1	< 0.1	< 0.1 - 1.9	0.1 - 7.7	0.1 - 5.7	0.1 - 3.5
Animal and vegetable fats and oils	0 - 0.1	< 0.1 - 0.1	< 0.1 - 0.2	< 0.1 - 0.2	< 0.1 - 0.2	< 0.1 - 0.3	< 0.1 - 0.3
Coffee, cocoa, tea and infusions	0	< 0.1 - 0.2	0.3 - 1.4	0.7 - 2.2	2.6 - 12.9	3.8 - 12.6	3.5 - 10.9
Composite dishes	0 - 0.7	0.6 - 10.7	0.2 - 10.4	0.5 - 13	0.7 - 13.6	1.3 - 12.2	1.5 - 11.9
Eggs and egg products	0.1 - 0.3	0.4 - 1.9	0.1 - 3	0.1 - 2.9	< 0.1 - 2.3	<0.1 - 2.3	0.1 - 2.1
Fish, seafood, amphibians, reptiles and invertebrates	0.3 - 1.1	1.5 - 3.9	1.2 - 5.9	1.2 - 6.3	2.3 - 6.9	3.4 - 10.2	4.1 - 12.7
Food products for young population	33.3 - 43.1	1.7 - 16.2	< 0.1 - 0.6	< 0.1 - 0.1	< 0.1	-[(a)]	-[(a)]
Fruit and fruit products	1.9 - 5.1	2.4 - 4.8	1.2 - 3.4	0.9 - 2.3	0.8 - 1.9	1.4 - 2.5	1.2 - 2.9
Fruit and vegetable juices and nectars	0.3 - 4.5	0.5 - 7.4	1 - 5.4	1 - 4.7	0.5 - 1.6	0.3 - 1.3	0.1 - 1.6
Grains and grain-based products	5.5 - 13	11.1 - 28.8	13.8 - 33.5	14.5 - 34	15.9 - 29.2	15.3 - 31.9	15.7 - 32.5
Human milk	< 0.1 - 39.8	< 0.1 - 1.3	-[(a)]	-[(a)]	-[(a)]	-[(a)]	-[(a)]
Legumes, nuts, oilseeds and spices	0.2 - 0.8	0.7 - 2	0.9 - 3.5	0.7 - 3.5	0.8 - 3.7	0.8 - 3.2	0.5 - 1.9
Meat and meat products	1.5 - 13.4	15.8 - 24	21.7 - 32.7	22.1 - 36.1	23.6 - 34.7	24.6 - 32.4	22.2 - 31.8
Milk and dairy products	8.7 - 32	19.1 - 33.7	12.1 - 30.2	9.3 - 23.2	7.2 - 14.5	6.9 - 14.1	7.3 - 10
Products for non-standard diets, food imitates and food supplements or fortifying agents	0 - 0.3	0 - 0.1	0.1 - 0.6	< 0.1 - 0.5	< 0.1 - 1.6	< 0.1 - 0.3	0 - 0.1
Seasoning, sauces and condiments	0.1 - 0.4	0.1 - 1.5	0.1 - 1.2	0.1 - 1.1	0.1 - 0.9	0.1 - 1	0.1 - 2
Starchy roots or tubers and products thereof, sugar plants	0.7 - 6.4	2.6 - 7	2.8 - 11.1	2.5 - 12.3	2.7 - 8.7	3.4 - 8.5	3.9 - 7.6
Sugar, confectionery and water-based sweet desserts	0 - 0.1	< 0.1 - 1.8	0.2 - 2.6	0.2 - 2.4	0.1 - 0.5	0.1 - 0.3	< 0.1 - 0.3
Vegetables and vegetable products	0.7 - 3.8	2.6 - 3.8	2.3 - 4.3	2.2 - 5.2	1.5 - 6	1.6 - 5.9	1.9 - 5.8
Water and water-based beverages	0	0 - 0.3	< 0.1 - 4.5	0.1 - 7.4	0.2 - 4.1	< 0.1 - 0.5	< 0.1 - 0.6

(a): '-' means that there was no consumption event of the food group for the age and sex group considered, while '0' means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

Appendix F. Minimum and maximum percentage contribution of different FoodEx2 level1 food groups to niacin intakes among females

Food groups	Infants	Children 1-< 3 years	Children 3-< 10 years	Adolescents 10-< 18 years	Adults 18-< 65 years	Adults 65-< 75 years	Adults ≥ 75 years
Additives, flavours, baking and processing aids	< 0.1	0 - 0.2	0 - 0.9	0 - 1.3	0 - 0.2	< 0.1	0
Alcoholic beverages	< 0.1	< 0.1	< 0.1	< 0.1 - 0.2	< 0.1 - 2	< 0.1 - 1.1	< 0.1 - 0.7
Animal and vegetable fats and oils	< 0.1 - 0.1	< 0.1 - 0.2	< 0.1 - 0.3	< 0.1 - 0.2	< 0.1 - 0.2	< 0.1 - 0.3	< 0.1 - 0.3
Coffee, cocoa, tea and infusions	0	< 0.1 - 0.2	0.2 - 1.5	0.6 - 3.8	3.9 - 13.6	4.7 - 13.5	5.5 - 11.2
Composite dishes	0 - 0.3	0.8 - 9.4	0.2 - 10.7	0.8 - 13.5	0.8 - 14.5	0.8 - 12.2	0.9 - 13.2
Eggs and egg products	< 0.1 - 0.5	0.4 - 2.2	0.1 - 3	0.1 - 2.9	0.1 - 2.1	0.1 - 2.1	0.1 - 2.4
Fish, seafood, amphibians, reptiles and invertebrates	0.2 - 4.5	1.3 - 8.2	0.5 - 4.7	1.1 - 7.6	3.1 - 7.9	4 - 11.1	4.7 - 11.7
Food products for young population	24.6 - 51.8	2.7 - 11.4	0.1 - 0.3	< 0.1 - 0.1	< 0.1	-[(a)]	< 0.1
Fruit and fruit products	2.7 - 5.1	2.4 - 4.4	1.5 - 3.7	1.2 - 3.5	1.4 - 2.8	2 - 3.5	1.9 - 3.7
Fruit and vegetable juices and nectars	< 0.1 - 1.8	0.5 - 5.1	0.8 - 5.2	0.8 - 4.1	0.4 - 1.7	0.4 - 1.5	0.4 - 1
Grains and grain-based products	6.2 - 13.2	11.7 - 30.5	14.4 - 32.8	16.7 - 33.5	16.8 - 30.3	14.8 - 28.5	15.2 - 31.7
Human milk	< 0.1 - 17.3	< 0.1	-[(a)]	-[(a)]	-[(a)]	-[(a)]	-[(a)]
Legumes, nuts, oilseeds and spices	0.2 - 1.9	0.6 - 1.9	0.9 - 2.7	0.8 - 2.7	1 - 2.7	1.1 - 2.3	0.8 - 1.2
Meat and meat products	3.6 - 12.2	17.8 - 21.6	20.5 - 31.5	22.3 - 32.8	22.9 - 32.9	20.9 - 31.8	20 - 33.6
Milk and dairy products	4.6 - 40.6	17.8 - 39.5	11.8 - 31.6	8.8 - 23.1	8.3 - 16.2	8.8 - 15.5	9.1 - 12.7
Products for non-standard diets, food imitates and food supplements or fortifying agents	0 - 0.3	0 - 0.4	0.1 - 0.7	< 0.1 - 0.6	0.1 - 1.4	< 0.1 - 0.6	0 - 1
Seasoning, sauces and condiments	0.1 - 0.2	0.1 - 0.9	0.2 - 1.2	0.1 - 1.2	0.1 - 1.2	0.1 - 1.3	0.1 - 1
Starchy roots or tubers and products thereof, sugar plants	2.8 - 6.2	3 - 6.2	3.1 - 12.2	3.2 - 11.9	3.1 - 7.6	3.8 - 6.4	3.7 - 6.6
Sugar, confectionery and water-based sweet desserts	0 - 0.5	< 0.1 - 1.7	0.3 - 2.5	0.3 - 2.6	0.1 - 1.2	0.1 - 0.4	0.1 - 0.5
Vegetables and vegetable products	1.7 - 4.1	2.5 - 4.1	2.2 - 5	2.2 - 5.3	2.4 - 6.4	2.5 - 7	2.6 - 6
Water and water-based beverages	0 - 0.1	0 - 0.3	< 0.1 - 4	0 - 5	< 0.1 - 3.2	< 0.1 - 0.5	< 0.1 - 0.1

(a): '-' means that there was no consumption event of the food group for the age and sex group considered, while '0' means that there were some consumption events, but that the food group does not contribute to the intake of the nutrient considered, for the age and sex group considered.

Appendix G. Summary of Population Reference Intakes (PRIs) for niacin for adults expressed in mg NE/day

Age	PRI at PAL = 1.4 (mg NE/day) [(a)]		PRI at PAL = 1.6 (mg NE/day) [(a)]		PRI at PAL = 1.8 (mg NE/day) [(a)]		PRI at PAL = 2.0 (mg NE/day) [(a)]	
	Men	Women	Men	Women	Men	Women	Men	Women
18-29 years	15.3	12.3	17.4	14.0	19.6	15.8	21.8	17.5
30-39 years	14.8	11.8	16.9	13.5	19.0	15.2	21.1	16.9
40-49 years	14.6	11.7	16.7	13.4	18.7	15.1	20.8	16.8
50-59 years	14.4	11.6	16.4	13.3	18.5	15.0	20.6	16.6
60-69 years	13.2	10.6	15.0	12.1	16.9	13.7	18.8	15.2
70-79 years	12.9	10.5	14.8	12.0	16.6	13.5	18.5	15.0

(a): The ARs for niacin in mg NE/day were calculated from the AR for niacin of 1.3 mg NE/MJ using the ARs for energy for adults according to the Scientific Opinion on Dietary Reference Values for energy (EFSA NDA Panel, 2013), and the PRIs were calculated assuming a CV of 10 %.

PAL: physical activity level.

Appendix H. Summary of Population Reference Intakes (PRIs) for niacin for infants aged 7-11 months expressed in mg NE/day

Age	PRI (mg NE/day) [(a)]	
	Boys	Girls
7 months	4.2	3.7
8 months	4.4	3.9
9 months	4.5	4.0
10 months	4.7	4.2
11 months	4.8	4.4

(a): The ARs for niacin in mg NE/day were calculated from the AR for niacin of 1.3 mg NE/MJ using the ARs for energy for infants aged 7-11 months according to the Scientific Opinion on Dietary Reference Values for energy (EFSA NDA Panel, 2013), and the PRIs were calculated assuming a CV of 10 %.

Appendix I. Summary of Population Reference Intakes (PRIs) for niacin for children and adolescents expressed in mg NE/day

Age	PRI at PAL = 1.4 (mg NE/day) [(a)]		PRI at PAL = 1.6 (mg NE/day) [(a)]		PRI at PAL = 1.8 (mg NE/day) [(a)]		PRI at PAL = 2.0 (mg NE/day) [(a)]	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
1 year	5.1	4.6						
2 years	6.7	6.2						
3 years	7.7	7.2						
4 years	8.2	7.6	9.4	8.7	10.5	9.8		
5 years	8.7	8.1	9.9	9.2	11.2	10.4		
6 years	9.2	8.6	10.5	9.8	11.8	11.0		
7 years	9.8	9.1	11.2	10.4	12.6	11.7		
8 years	10.4	9.6	11.9	11.0	13.4	12.4		
9 years	11.0	10.2	12.6	11.7	14.1	13.1		
10 years			12.6	11.9	14.2	13.4	15.8	13.4
11 years			13.3	12.5	15.0	14.0	16.7	14.0
12 years			14.2	13.1	16.0	14.7	17.7	14.7
13 years			15.2	13.7	17.1	15.4	19.0	15.4
14 years			16.4	14.2	18.5	16.0	20.5	16.0
15 years			17.6	14.5	19.8	16.4	22.0	16.4
16 years			18.6	14.7	20.9	16.6	23.2	16.6
17 years			19.2	14.9	21.6	16.7	24.0	16.7

(a): The ARs for niacin in mg NE/day were calculated from the AR for niacin of 1.3 mg NE/MJ using the AR for energy for children and adolescents according to the Scientific Opinion on Dietary Reference Values for energy (EFSA NDA Panel, 2013), and the PRIs were calculated assuming a CV of 10 %.

PAL: physical activity level.

Appendix J. Summary of Population Reference Intakes (PRIs) for niacin for pregnant and lactating women (in addition to the PRI for non-pregnant non-lactating women) expressed in mg NE/day

	PRI [(a)] (mg NE/day)
Pregnant women	
1st trimester	+ 0.5
2nd trimester	+ 1.7
3rd trimester	+ 3.3
Lactating women	
0-6 months post partum	+ 3.3

(a): The additional ARs for niacin in mg NE/day were calculated from the AR for niacin of 1.3 mg NE/MJ using the AR for additional energy for pregnancy or lactation (i.e. in addition to the AR for energy for non-pregnant non-lactating women) according to the Scientific Opinion on Dietary Reference Values for energy (EFSA NDA Panel, 2013), and the PRIs (to be added to the PRI for non-pregnant non-lactating women) were calculated assuming a CV of 10 %.

ABBREVIATIONS

2-Pyr	*N*-methyl-2-pyridone-carboxamide
4-Pyr	*N*-methyl-4-pyridone-carboxamide
Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
ATP	Adenosine triphosphate
COMA	Committee on Medical Aspects of Food Policy
CV	Coefficient of Variation
D-A-CH	Deutschland-Austria-Confoederatio Helvetica
DIPP	Diabetes Prediction and Prevention Nutrition Study (DIPP)
DNA	Deoxyribonucleic acid
DH	Department of Health
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
EsKiMo	Ernährungsstudie als KiGGS-Modul
EU	European Union
FAO	Food and Agriculture Organization
FINDIET	The National Dietary Survey of Finland
HD	Hospital diet
hOAT10	Human organic anion transporter 10
INCA	Étude Individuelle Nationale des Consommations Alimentaires
INRAN	Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione
IOM	U.S. Institute of Medicine of the National Academy of Sciences
LTI	Lowest Threshold Intake

NAD	Nicotinamide adenine dinucleotide
NADH	Reduced nicotinamide adenine dinucleotide
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NANS	National Adult Nutrition Survey
NDNS	National Diet and Nutrition Survey
NE	Niacin equivalent
NL	Health Council of the Netherlands
NMN	*N*-methyl-nicotinamide
NNR	Nordic Nutrition Recommendations
NOAEL	No Observed Adverse Effect Level
NWSSP	Nutrition and Wellbeing of Secondary School Pupils
PAL	Physical activity level
PRI	Population Reference Intake
RDA	Recommended Dietary Allowance
RI	Recommended Intake
SCAI	Studio sui Consumi Alimentari in Italia
SCF	Scientific Committee for Food
UL	Tolerable Upper Intake Level
VCP	Voedselconsumptiepeiling
VELS	Verzehrsstudie zur Ermittlung der Lebensmittelaufnahme von Säuglingen und Kleinkindern für die Abschätzung eines akuten Toxizitätsrisikos durch Rückstände von Pflanzenschutzmitteln
WHO	World Health Organization