

EXPERT GROUP ON VITAMINS AND MINERALS

REVIEW OF NIACIN – REVISED VERSION

The attached review of niacin is an updated version of the paper initially presented to the Expert Group on Vitamins and Minerals at the meetings on 2 April 2001 and 29 June 2001. New information has been incorporated into the review to take account of comments made by Members and to correct a number of minor inaccuracies.

The following annexes are also included:

- Annex 1 Tables referred to in the review
- Annex 2 Intakes of niacin from foods and supplements
- Annex 3 Summary table of selected nutrition related information and existing guidance on intakes

Expert Group on Vitamins and Minerals Secretariat
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NIACIN

Chemistry

1. 'Niacin' (Vitamin B₃) is the generic term for nicotinic acid, nicotinamide, and the coenzyme forms of the vitamin; where no form is specified the term niacin is used. Nicotinamide is the active form of the vitamin, which functions as a constituent of two coenzymes, namely, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes in their reduced states (NADH/NADPH) are the principal forms of niacin that exist in animal tissues. In North America, niacin often refers exclusively to nicotinic acid, thus causing some confusion between the generic and specific terms.
2. Nicotinic acid (pyridine 3-carboxylic acid) and nicotinamide (nicotinic acid amide) have molecular weights of 123 and 122.1 respectively. Both compounds are stable, white crystalline solids. Nicotinamide is more soluble in water, alcohol and ether than nicotinic acid.

Natural occurrence

3. Free nicotinic acid and nicotinamide are present in nature in only small amounts and are frequently found in their bound forms. Nicotinic acid is found mainly in plants, where it is often bound to macromolecules, however, nicotinamide is found primarily in the animal world, in by far the largest amounts as a component of NADP (Henderson, 1983).
4. Humans are able to synthesise niacin *de novo* from dietary tryptophan, and it has been reported that normal intakes of tryptophan are adequate to meet niacin requirements without the need for any preformed niacin in the diet, assuming unimpaired metabolism of tryptophan (Bender, 1992). In consideration of this interrelationship, the niacin content of foods is usually expressed as niacin equivalents (NE). This is calculated from the amount of niacin present plus 1/60th of the amount of tryptophan. The factor of 1/60th was derived from the amount of tryptophan considered to be equivalent to 1 mg of nicotinic acid. Niacin equivalents are generally expressed as mg/1000kcal. Although niacin is endogenously synthesised in the body, it is still categorised as a vitamin. This is because its precursor, tryptophan, is an essential amino acid and the ultimate synthesis of niacin is thus dependent upon the diet (Basu and Dickerson 1996).

Occurrence in food, food supplements and medicines

Food

5. Important sources of preformed niacin include beef (23.80 NE), pork (2.17 NE), wheat flour (7.43 NE), maize (corn) flour (6.74 NE), eggs (19.80 NE), and cow's milk (12.40 NE) (Basu and Dickerson 1996). In uncooked foods, niacin is present mainly in the

form of the cellular pyridine nucleotides NAD and NADP. Enzymatic hydrolysis of the coenzymes can occur during the course of food preparation, this is due mostly to the widely occurring NAD(P)⁺ glycohydrolases and pyrophosphatases (Henderson, 1983).

6. In cereals, niacin is present in covalently bound complexes with small peptides and carbohydrates as a complex defined as 'niacytin' (Mason *et al* 1973). The esterified niacin contained within these complexes is normally unavailable for absorption, however, the bioavailability of niacin can be increased by pre-treatment with alkali to hydrolyse the esters. Maize (corn) also contains appreciable amounts of niacin, this niacin is in a bound state and is biologically unavailable, but it can be released upon roasting (Kodicek *et al* 1974). In some other foods, for example coffee, niacin is present as a methylated derivative called trigonellin (1-methylnicotinic acid) which functions as a plant hormone. Nicotinic acid is liberated in coffee by roasting, this process removes the methyl group from the trigonellin, forming nicotinic acid. The result is an increase in the nicotinic acid concentration in the coffee bean from 20 mg/kg to a maximum of 500 mg/kg (Smith 1963).
7. Human milk contains a higher concentration of preformed niacin than cow's milk and a lactating woman typically secretes between 1.0-1.3 mg of preformed niacin daily in 750 ml of milk (National Research Council 1989).
8. In the UK there is mandatory fortification of flour except wholemeal and certain other specified types with nicotinic acid at a level of not less than 1.6 mg/100 g flour for restoration purposes. Expert reports to Government, (MAFF 1974 and COMA 1981) have recommended that compulsory fortification of flour was no longer necessary but it remains in force.

Food supplements

9. In the UK, niacin supplements are generally in the form of nicotinamide. Data from UK dietary surveys (see Annex 2) indicate that dietary supplements made a significant contribution to average intakes for adult women and older women living in the community.
10. Dietary supplements containing niacin provided very little niacin for young people aged 4-18 years, contributing less than 1% of mean intake. In children aged 1½-4½ years, supplements contributed 2% to mean niacin intakes.
11. In adults, supplements provided 6% of mean intake of niacin equivalent for females and 2% for males. For older people free-living in the community dietary supplements provided 2% of intakes from all sources for men and 5% for women. For older people living in institutions the contribution was much smaller, 1% of mean intakes. Of course, the proportion of intake from supplements is much higher if supplement consumers are considered separately.
12. Declared levels for nicotinamide supplements range from 100-250 mg (see EVM/00/05.revised). Nicotinamide levels in multi-nutrient supplements range from

0.25 to 150 mg with 18-50 mg being most commonly available. Nicotinic acid is not available as a single supplement but may be present in multi-nutrient supplements at levels 2 to 10 mg with 10 mg being most commonly available.

Licensed medicinal products for oral use

Nicotinic acid

13. Two multi-vitamin products containing nicotinic acid may be sold in supermarkets and other retail outlets, without the supervision of a pharmacist, for the prevention of deficiency. The maximum daily doses authorised are up to 100 mg, which is also the maximum allowed under the Medicines (General Sales List) Order, 1984.
14. Products that can only be sold under the supervision of a pharmacist include a product with a maximum daily dose of 40 mg for night muscle cramp.
15. Eight single nutrient nicotinic acid products are available for use in hyperlipidaemias (generally specified as Type IIA, IIB or IV) if prescribed by a doctor. The maximum daily dose is 6000 mg.

Nicotinamide

16. Thirty-four multi-vitamin products and one single nutrient product containing nicotinamide are authorised for sale in supermarkets and other retail outlets, without the supervision of a pharmacist, for the prevention and treatment of deficiencies. The maximum daily doses authorised for these products are up to 300 mg, which is also the maximum daily dose allowed under the Medicines (General Sales List) Order, 1984.
17. Products that can only be sold under the supervision of a pharmacist include 32 multivitamin products and one single nutrient product for the prevention and treatment of deficiencies. The maximum daily doses authorised for these products are up to 500 mg.
18. One multivitamin product containing nicotinamide is used for the treatment of specific metabolic disorders and by those on special diets. It is only available on prescription.

Intake and exposure

Food

19. In the Dietary and Nutritional Survey of British Adults (1990) mean niacin intakes were 39.9 and 28.5 mg niacin equivalent/1000 kcal in men and women respectively. The contribution made by supplements was very small and average intakes including supplements were similar to average intakes from food only (see annex 2). In young people aged 15-18 years the main sources of niacin in the diet were found to be cereals, cereal products, meat and meat products which provided over a third of their average

intake. Vegetables, potatoes and savoury snacks provided 12% of niacin equivalent intake, of which nearly a half came from potatoes.

Recommended amounts

20. The Committee on Medical Aspects of Food and Nutrition Policy (COMA) (1991) has set a Reference Nutrient Intake (RNI) for nicotinic acid equivalent (niacin) of 17 mg/day for males and 13 mg/day for females 19-50 years.
21. The recommended dietary allowance (RDA) for adults is 15 to 20 mg of niacin daily (FAO/WHO Group 1967). Under normal conditions, for an adult, the amount of tryptophan present in dietary protein provides adequate niacin without the need for any preformed vitamin. For example, in the UK, median protein intake has been estimated to be 84.0 g/day by men and 61.8 g/day by women (Gregory *et al* 1990). At an equivalence of 60 mg tryptophan : 1 mg of niacin, this alone is equivalent to 17.6 mg/day for men and 13.0 mg/day for women (Basu and Dickerson 1996).

Bioavailability

22. In a human study involving nine healthy adult men and women, the bioavailability of niacin in maize bran supplements produced by wet milling and dry milling processes was investigated. The bioavailability of niacin in dry-milled maize bran was slightly higher (2.33%) than in wet-milled maize bran (1.70%). Examination of the effect of particle size, regardless of type of milling, revealed that coarse bran (1.86%) gave significantly ($p < 0.05$) lower utilisation of niacin than fine maize bran (2.17%) (Yu and Kies, 1993).
23. Roth Maier *et al* (2000), investigated the apparent precaecal digestibility of niacin from human foods including wheat, wholemeal bread, boiled potatoes, and boiled pork and beef, in female pigs. Pigs were subjected to an end-to-end ileo-rectal anastomosis so digesta passed straight from the ileum to the rectum eliminating endogenous vitamin synthesis. The intestinal bioavailability of niacin was affected differently by the food administered. The digestibility values of niacin deriving from the wheat- potato- and meat-based meals ranged from 59 to 69%. Wholemeal bread exerted a nutritionally important negative effect on the apparent intestinal availability of dietary niacin relative to other foods, which averaged by 40%.

Interactions

Alcohol

24. An unusual case of delirium and lactic acidosis was reported in a 44 year old male receiving nicotinic acid therapy (3 g/day) for hypercholesteremia, following the ingestion of 1 litre of red wine 24h prior to presentation. It was postulated that the

syndrome was precipitated by ethanol ingestion in the setting of pre-existing hepatic dysfunction secondary to nicotinic acid use (Schwab and Bachhuber, 1991).

Drug interactions

25. Prolonged treatment with the drug Isoniazid may lead to a niacin deficiency due to competition of the drug with pyridoxal phosphate, a coenzyme required in the tryptophan to niacin pathway (Jacob and Swendseid 1996).
26. Enhanced vasodilation may occur upon co-administration of nicotinic acid and ganglionic blocking agents used in the treatment of hypertension (Yewshurun and Gotto 1976).
27. Clonidine may inhibit nicotinic acid-induced vasodilation, thus inhibiting skin flushing. This is potentially a favourable interaction if the concurrent use of clonidine is indicated for hypertension (Sigroth 1974).

Function

28. Niacin is the functional component of two important coenzymes, NAD and NADP (nicotinamide adenine dinucleotide and its phosphorylated relative), which activate over 200 dehydrogenase enzymes essential to electron transport and other cellular respiratory reactions. Most dehydrogenases are specific to either NAD or NADP, however, a small number of dehydrogenases use both nicotinamide coenzymes (Levy *et al* 1983).
29. In spite of their great structural similarity, NAD and NADP have quite different metabolic roles. NAD functions as an electron carrier for intracellular respiration as well as a co-dehydrogenase with enzymes involved in the oxidation of fuel molecules, such as glyceraldehyde 3-phosphate, lactate, pyruvate and α -ketoglutarate dehydrogenases. NADP functions as a hydrogen donor in reductive biosyntheses, such as in fatty acid and steroid syntheses, and like NAD as a co-dehydrogenase, such as in the oxidation of glucose-6-phosphate to ribose 5-phosphate in the pentose phosphate pathway (Jacob and Swendseid 1996).
30. The niacin co-factor NAD is also required for important non-redox reactions. It is the substrate for three classes of enzymes that cleave the β -N-glycosylic bond of NAD to free nicotinamide and catalyse the transfer of ADP-ribose to proteins (Jacob and Swendseid, 1996).

Deficiency

Human

31. Among the most common causes of a niacin deficiency are an unbalanced diet (e.g. an excess of maize) and vitamin B₆ deficiency; vitamin B₆ is necessary for the conversion of tryptophan to niacin. Medications can also cause niacin deficiency, for example, Parkinson syndrome patients treated with L-dopa often suffer from niacin deficiency (Bender *et al* 1979).
32. The most common symptoms of a niacin deficiency are divided into three categories: changes in the skin; changes in the mucosa of the mouth, stomach and intestinal tract; and changes in the nervous system. The changes in the skin are among the most characteristic in human beings. They are called 'pellagra', which means 'raw skin'. These symptoms are most pronounced in parts of the skin which are exposed to sunlight. Depending on the degree of severity, the deficiency can be expressed as dizziness, vomiting, constipation or diarrhoea. In severe deficiency, the human tongue and gastric mucosa become inflamed; the tongue becomes bright red and swells. The neurological symptoms experienced can include fatigue, sleeplessness, depression, loss of memory and visual impairment (Gopalan and Rao, 1975).

Animal

33. Feeding a diet deficient in nicotinamide, nicotinic acid and tryptophan to pregnant rats from the first day of conception, causes death and resorption of all foetuses consistent with a decreased concentration of NAD in maternal liver (Fratta *et al* 1964).

Overview of reported non-nutritional beneficial effects

34. Human volunteer studies have shown that supplementation of the diet with nicotinic acid (100 mg/day) for 8 weeks results in an approximate five-fold increase in NAD⁺ concentrations in lymphocytes. DNA-strand breaks in lymphocytes exposed to oxygen radicals were shown to decrease proportionately to NAD⁺ concentrations over this period, indicating that *in vivo* supplementation with nicotinic acid may represent a strategy for protecting against oxygen radical-induced genetic damage (Weitberg 1989).
35. Nicotinic acid at concentrations of 0.1 to 10 mM has been shown to reduce oxygen toxicity in mouse alveolar macrophages, suggesting it may be of clinical value in reducing pulmonary oxygen toxicity (Pearl and Raffin, 1983).
36. Nicotinic acid has been shown to reduce total cholesterol and low density lipoprotein cholesterol levels by an average of 20 to 30%, triglyceride levels by 35 to 55%, and increase high density lipoprotein cholesterol levels by 20 to 35% (Berge *et al* 1961, Christensen *et al* 1961, Knopp *et al* 1985, Alderman *et al* 1989). These findings have led to the use of nicotinic acid in the treatment of hypercholesterolemia. In one study, treatment of hypercholesteremic patients with nicotinic acid (4 g/day) was reported to reduce plasma cholesterol in 41 out of 51 cases, with mean levels of plasma cholesterol decreasing from 314 mg per 100 ml to 201 mg (Brown and Goldstein, 1975). The lipid-decreasing effects of nicotinic acid have been extensively investigated, but the

mechanism of action is not known. However, it does not appear to be related to vitamin coenzyme function since nicotinamide does not have a similar effect (Chiu, 1961).

37. A co-operative study in the US (Canner *et al* 1986) retrospectively considered patients who had participated in the Coronary Drug Project (1975), a study originally designed to investigate the use of nicotinic acid in coronary heart disease. The study concluded that nicotinic acid reduced mortality by 11% (vs. placebo) ($p < 0.0004$). The reduction in mortality was due to a reduction of lethal coronary events. Blakenhorn and associates (1987), and Brown and colleagues (1989), reported that the combination of niacin and a bile acid sequestrant results in a lower incidence of progression and a higher incidence of regression of coronary atherosclerosis in angiographic studies.
38. Nicotinamide in a dosage of approximately 25 mg/kg/day is currently under trial for helping prevent and control diabetes (Mandruppoulsen *et al* 1993). It has been shown to offer protection in recognised experimental models of immune-mediated insulin-dependent diabetes mellitus (IDDM) (Reddy *et al* 1990). In addition, three of six placebo-controlled studies in recent onset IDDM individuals showed a positive effect of nicotinamide in terms of prolonged non-insulin-requiring remission, lower insulin requirement and increased β -cell function (Vague *et al* 1987).
39. A study that investigated the relationships between a wide range of macro- and micronutrients and the three main types of cataract in older people aged 49 to 97 years (N=2900) found that higher intakes of niacin (form not stated) were associated with reduced prevalence of nuclear cataract. After adjusting for multiple known cataract risk factors, the odds ratios for those in the highest quintile were 0.5 (95% confidence interval [CI], 0.3 – 0.8).

Absorption

Human

40. In humans, niacin is rapidly absorbed from the stomach, intestine (Bechgaard and Jespersen 1977), and through the cheek mucosa (Evered *et al* 1980), by a sodium, carrier-mediated mechanism at low concentrations. However, this mechanism does not apply to pharmacological doses of the vitamin. After oral application of 3.0 grams of nicotinic acid per day, approximately 85% of the vitamin is found in the urine, indicating absorption occurs through the intestine by passive diffusion (Hankes 1984).
41. Background serum nicotinic acid levels (from dietary intake) range from 1 to 2 $\mu\text{g/ml}$ (Robinson *et al* 1978). Peak serum levels after ingestion of 1 gram of standard formulation nicotinic acid range from 15 to 30 $\mu\text{g/ml}$ (Miller *et al* 1960, Carlson *et al* 1968). The time required to reach peak plasma level, ranged from 30-60 minutes (Carlson *et al* 1968).

42. The plasma half-life of nicotinic acid is relatively short, approximately 1 hour (Pettrack *et al* 1966).

Animal

43. Experiments utilising inverted rat intestinal sacs indicate that niacin is rapidly absorbed in the stomach and small intestine. At low concentrations absorption occurs via a sodium-dependent, carrier-mediated facilitated diffusion process. At higher concentrations, as in humans, passive diffusion dominates (Sadoogh-Abasian and Evered 1980).

44. In tissue investigations using radiolabelling, no free nicotinic acid could be detected either in the liver or in the fat tissue of rats 6 hours after a subcutaneous injection of nicotinic acid (250 mg/kg) (Carlson and Nye 1966).

Distribution

45. NAD and NADP, the main dietary forms of niacin, are hydrolysed by enzymes in the intestinal mucosa and liver to yield nicotinamide. The intestinal mucosa and liver are rich in niacin conversion enzymes such as NAD glycohydrolase. Nicotinamide, the major form of niacin in the bloodstream, is released from NAD in the liver and intestines and transported to tissues that synthesise their own NAD as required (Jacob and Swendseid, 1996).

46. Niacin circulates in the plasma as unbound forms of both the acid and the amide. Each enters peripheral tissues by passive diffusion, followed by metabolic trapping by conversion to the pyridine nucleotide NAD(H) and NADP(H). Most is found as NAD(H) and in the oxidised form (NAD). In contrast, most of the NADP is found in the reduced form (NADPH). The majority of mammalian organs can use either nicotinic acid or nicotinamide to synthesise NAD, but a few can use only nicotinamide (Henderson, 1983).

47. Nicotinic acid is taken up into erythrocytes via their anion-transport system, and accumulates to high concentrations, reaching a concentration ratio of whole blood to serum of 100:1 and higher (Frank *et al* 1963). Nicotinic acid is converted to NAD by the Preiss-Handler pathway, and converted to nicotinamide by NAD(P)⁺ glycohydrolase which enters the circulation and serves as the precursor of NAD in other organs which cannot utilise nicotinic acid.

48. Animal studies have shown that nicotinic acid rapidly disappears from the blood compartment and is mainly concentrated in the liver, but also in the adipose tissue and in the kidneys (Carlson and Hanngren, 1964).

Metabolism

49. The quantitative composition of niacin metabolites in man is dependent upon the dose administered, but the principal metabolites under basal conditions are *N*-methyl-nicotinamide, *N*-methyl-2-pyridone-5-carboxamide, and *N*-methyl-4-pyridone-5-carboxamide. *N*-methyl-2-pyridone-5-carboxamide appears to be the end product of niacin metabolism in man (Goodman and Gilman, 1975).
50. After rapid amidation in the liver, the nicotinamide that is produced is *N*-methylated with the participation of ATP and Mg^{2+} , and oxidised to the 2- or 4-pyridone derivative by aldehyde dehydrogenase. In addition, *N*-ribosyl-2-pyridone-5-carboxamide is produced from the nucleotide metabolism as a degradation product (Mrocheck *et al* 1976).
51. Interspecies variation in the metabolism of niacin is known to occur. For example, *N*-methyl-2-pyridone-5-carboxamide, which is a quantitatively important metabolite in man, hardly occurs in dogs, cats, sheep, or rats (Chang and Johnson 1962). Nicotinamide-*N*-oxide, a principal metabolite in mice, occurs in only minor levels in man (Chaykin *et al* 1965).

Excretion

Humans

52. The pattern of niacin products excreted after ingestion of the vitamin depends largely on the amount and form of niacin ingested and the niacin status of the individual. However, the two major excretion products in man are *N*-methylnicotinamide and *N*-methyl-2-pyridone-5-carboxamide, with minor amounts of niacin or niacin oxide and hydroxyl forms also being excreted. After administration of a pharmacological dose of nicotinic acid, nicotinic acid and *N*-methyl-2-pyridone-5-carboxamide in the urine are greatly elevated (Mrocheck *et al* 1976).
53. The ratio of *N*-methyl-2-pyridone-5-carboxamide to *N*-methylnicotinamide is held, by some workers, to be a reliable indicator of niacin status. The ratio is usually 1.3 to 4.0, with values of less than 1.0 indicating a niacin deficiency (Hankes 1984). However, the reliability of this ratio falls into question, since quantitative data for excretion of urinary metabolites have not been standardised (Jacob *et al* 1989).
54. Elevated renal excretion of *N*-methylnicotinamide and *N*-methyl-2-pyridone-5-carboxamide is observed in pregnant women. It is thought that the elevated excretion of the metabolites observed is the result of an increased utilisation of niacin and an increased conversion of tryptophan to niacin. In diabetics, the excretion of *N*-methyl-2-pyridone-5-carboxamide is significantly reduced, whereas that of *N*-methylnicotinamide is practically unchanged. In humans suffering from niacin deficiency 'pellagra', the renal excretion of both metabolites is reduced serving as an index of niacin deficiency (Barlow *et al* 1977).

Animals

55. Feeding of radiolabelled niacin to animals allowed the discovery of a whole spectrum of urinary excretion products. These include nicotinic acid, nicotinamide, 1-methylnicotinamide, nicotinamide 1-oxide, 1-methyl-4-pyridone 3-carboxamide, 1-methyl-6-pyridone 3-carboxamide, nicotinuric acid, 6-hydroxynicotinamide and 6-hydroxynicotinic acid (Henderson, 1983).

Toxicity

56. Reports of nicotinic acid toxicity in humans stem, in the main, from its use in the treatment of hypercholesterolemia. Most adverse effects are dose related and generally subside with a reduction in dosage or the cessation of treatment. Vitamin toxicities resulting from foodstuffs are known to occur, but they are rare.

Human toxicity*Acute toxicity – nicotinic acid*

57. Flushing is the commonest side effect of nicotinic acid therapy and occurs at even low therapeutic doses of the drug (Hathcock 1997, Rader *et al* 1992). Tolerance to this effect, known to be prostaglandin-mediated (Olsson *et al* 1983), usually develops over several weeks and can be significantly reduced by co-administration of aspirin (Nozaki *et al* 1987).
58. In a study by Spies *et al* (1938) subjects were given single oral doses of 50 or 100 mg nicotinic acid. Flushing was reported in 5% of those receiving the 50 mg dose and 50 % of those given 100 mg.
59. Two cases of anaphylactic shock caused by sensitivity to nicotinic acid were reported by Perner (1946). The first case, a 34 year old woman, received a single intravenous injection of nicotinic acid (50 mg per c.c.), within two minutes the patient became short of breath and was in a state of collapse. It was concluded that she had been sensitised to nicotinic acid through previous medication with nicotinic acid amide by mouth. In a second case, nicotinic acid therapy was initiated in a 25 year old female for the treatment of chronic headaches. No adverse effects were reported on the first, second and third days of therapy following intravenous administration of 5 mg, 10 mg, and 15 mg of nicotinic acid respectively. On the fourth day, 20 mg of the drug was administered intravenously. Within several minutes the patient became dizzy, short of breath, and went into shock.
60. Watrous (1939) reported four cases of severe itching and diffuse erythema of the skin in industrial workers exposed to nicotinic acid, however, other workers exposed under the same conditions exhibited no reaction. Powdered nicotinic acid rubbed into the skin of workers elicited itching and erythema in a number of cases, but this result was not

evident in others, suggesting some workers were sensitive to nicotinic acid and some were not.

61. In 1960, an outbreak of food poisoning due to sodium nicotinate was reported at the Northwestern University, USA. Of the 121 people dining at the sorority house, 39 female and 5 male students developed symptoms, including a diffuse feeling of warmth, itching of the skin, redness, and flushing of the face, 20 to 40 minutes after they began to eat. Analysis of a sample of ground meat remaining from the evening meal revealed a concentration of 225 mg of sodium nicotinate per 100 grams of cooked meat. It was later learned that prior to fine grinding approximately 2% of powdered nicotinate had been sprinkled on the meat. It was concluded that the uneven dispersion that ensued during grinding, together with the varying susceptibility of the individuals, accounted for the fact that only 44 out of 121 persons concerned noted symptoms (Press and Yeager, 1962).
62. According to one report, eating pumpernickel bagels containing approximately 190 mg of nicotinic acid caused rashes, pruritus, and sensations of warmth in 14 out of 25 people (CDC, 1983).
63. Ferencik and Rovner (1989) reported a case involving a patient who presented with hematemesis, elevated prothrombin time and abnormal liver function tests after self-administering nicotinic acid (6 g/day) for a period of just one week. This case is unique because toxic hepatitis is usually reported in patients taking nicotinic acid for prolonged periods of time, typically months to years.
64. There are no reports of acute toxicity with nicotinamide in man.

Sub-chronic and chronic toxicity – nicotinic acid

65. Sebrell and Butler (1938) examined dose response in groups of six subjects given 10, 30 or 50 mg nicotinic acid daily for three months, in subjects in these groups flushing was reported intermittently, in 0, 2 and 4 individuals, respectively.
66. There have been numerous reports associating nicotinic acid therapy with hepatotoxicity, however, this appears to be a rare complication that usually only occurs following the ingestion of more than 3 g/day over extended periods of time. In most cases toxicity is evidenced as jaundice, pruritus, and mild elevations in serum bilirubin, alkaline phosphatase, and aminotransferase levels that resolve within one month of drug cessation (Rivin 1959, Pardue 1961, Parsons 1961, Sugarman and Clark 1974, Einstein *et al* 1975, Clementz and Holmes 1987).
67. During the course of a study conducted by the Coronary Drug Project Research Group (1975), one-third to one-half of patients taking 3 grams of nicotinic acid per day for 5 years were found to have elevated levels of serum glutamate oxalacetate transaminase (SGOT) and alkaline phosphatase.

68. Hoeg *et al* (1984) investigated the effect of combined neomycin (2 g/day) and nicotinic acid (3 g/day) treatment on plasma lipoprotein concentrations in 25 type II hyperlipoproteinemic patients in a double-blind, placebo-controlled clinical trial. Eleven patients (44%) were unable to continue nicotinic acid treatment because of adverse side effects including abdominal pain, flushing, rash and nausea. Routine blood analyses showed that the addition of nicotinic acid to the regimen resulted in statistically significant ($p < 0.05$) increases in the concentration of liver enzymes.
69. In one report, jaundice occurred in a 69 year old man following ingestion of a dose of nicotinic acid as low as 750 mg per day for only 3 months. The jaundice became more severe in the three weeks following discontinuation of the drug but began to recede within a month (Sugarman and Clark, 1974).
70. Clementz and Holmes (1987) reported a case of modest hepatocellular injury in a 46 year old male receiving nicotinic acid (3 g/day) therapy for one month for the treatment of hypercholesterolemia. Therapy was terminated for six weeks and then reinstated for a further ten weeks, after which the patient presented with fulminant hepatic failure which subsequently resolved rapidly upon withdrawal of treatment.
71. One individual was reported to develop hypoalbuminemia, oedema, and abnormal liver function after having received nicotinic acid (3 g/day) for six months. Improvement was progressive following cessation of the drug (Pardue 1961).
72. Einstein and colleagues (1975) described a case of acute hepatitis with evidence of submassive necrosis in a woman who had taken 3 grams of nicotinic acid per day for two and a half years for psychological disturbance. Electron micrographs of biopsy material revealed dilatation of the smooth endoplasmic reticulum (ER) and vesicle formation. The patient recovered on discontinuation of therapy.
73. Although most hepatic illness is mild and self-limiting, there have been reports of severe hepatic dysfunction associated with nicotinic acid and nicotinamide therapy. Patterson *et al.*, (1983) reported a case of severe liver injury occurring on two occasions in a patient taking self-prescribed nicotinic acid for the treatment of depression. The patient developed modest hepatotoxicity after taking nicotinic acid (4.5 g/day) for six months. This was followed by a much more severe episode of liver injury when he later reinstated nicotinic acid therapy and added 3 grams daily of nicotinamide (see paragraph 87). Liver biopsy revealed distortion of liver architecture, massive and submassive lobular collapse and marked cholestasis.
74. Sustained-release (SR) nicotinic acid preparations are increasingly utilised to treat hyperlipidemia due to a lower incidence of flushing and convenient dosing frequency. Interestingly, it has been suggested that the sustained-release form of nicotinic acid may be associated with more extensive hepatocellular injury than the crystalline preparation (Knopp *et al* 1985, Mullin *et al* 1989, Henkin *et al* 1990, Hodis 1990, McKenney *et al* 1994, Gibbons *et al* 1995).

75. Mullin *et al* (1989) reported a case of a 44 year old male receiving therapy with crystalline nicotinic acid (6 g/day) for hypercholesterolemia. The patient received the therapy for 5 months with no adverse side effects. Following transfer to sustained-release nicotinic acid therapy at an identical dose, the patient developed jaundice and grade II hepatic encephalopathy.
76. A similar case, documented by Hodis (1990) described how a 32 year old male taking over the counter super-timed release nicotinic acid (500 mg/day) for 2 months developed grade IV hepatic encephalopathy.
77. One report describes three patients who developed hepatitis during treatment with sustained-release nicotinic acid. Interestingly, rechallenge with equivalent or higher doses of crystalline nicotinic acid revealed no evidence of recurring hepatocellular damage (Henkin *et al* 1990).
78. Knopp *et al* (1985) conducted a study involving 71 hyperlipidemic patients, comparing the effects of unmodified nicotinic acid (Nicolar) and sustained release nicotinic acid (Nicobid). Treatment was for six months and subjects received an initial dose of 1.5 g/day increasing to 3 g/day from the second month onwards. Subjects treated with Nicobid experienced a significantly higher ($p < 0.05$) rate of gastrointestinal effects compared with subjects treated with Nicolar. However, both preparations lowered serum cholesterol and low density lipoprotein cholesterol levels equally.
79. Gibbons *et al* (1995) conducted a study to investigate the prevalence of side effects that occur with the use of regular and sustained-release nicotinic acid. In total 110 patients participated over a five year period. 43% of the individuals given regular nicotinic acid and 42% of those given the sustained-release formulation had to discontinue the medication due to adverse side effects. The symptoms reported included flushing, nausea, vomiting, abnormal liver function tests, elevated uric acid and elevated serum glucose.
80. McKenney *et al* (1994) conducted a randomised, double-blind study to compare the effects of immediate-release (IR) and sustained-release (SR) preparations of nicotinic acid in 46 adults. During the course of the study 39 per cent of the patients receiving the IR formulation withdrew due to vasodilatory symptoms and acanthosis nigricans. Seventy eight per cent of the patients assigned to the SR group also withdrew mainly due to gastrointestinal related symptoms and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction. None of the patients receiving IR nicotinic acid developed hepatotoxic effects, while 52% of the SR group did.
81. The Coronary Project Research Group (1975) conducted a study to investigate the possible use of nicotinic acid in coronary heart disease to reduce the incidence of a second myocardial infarction. The study demonstrated very little immediate benefit, but considerable toxicity, showing a greater incidence of atrial fibrillation and other cardiac arrhythmias. At 3 grams per day over a five year period, 2.6 percent of men on nicotinic acid ($n = 994$) had arrhythmias compared to only 1.3 percent on placebo ($n = 2517$).

Nicotinic acid has been found to inhibit the use of free fatty acids by the heart, leading to an undesirable effect on the metabolism of heart muscle (Lassers *et al* 1972).

82. Deterioration of oral glucose tolerance is commonly observed during therapy with nicotinic acid. In one study, six diabetic patients who had been taking 1-3 g of nicotinic acid per day for 5-6 months developed hyperglycemia, glucosuria, ketonuria and increased free fatty acid (Molnar *et al* 1964). Schwartz (1993) reported a case of hyperglycemia in a patient receiving nicotinic acid therapy for hypercholesterolemia. Following 4 months of therapy at 3 g/day the patient presented with polyuria, anorexia, fatigue and elevated blood glucose (1046 mg/dl). The patient demonstrated no evidence of glucose intolerance following discontinuation of nicotinic acid therapy.
83. Parsons (1960) reported an increased incidence of duodenal ulcers after 96-130 weeks of nicotinic acid (3-7.5 g/day) therapy. However, most of the reported patients had a previous history of ulcer symptoms.
84. Nicotinic acid may increase serum uric acid levels. The Coronary Drug Project Research Group (1975) found an increase in the incidence of gouty arthritis in patients on nicotinic acid. Forty-four per cent of patients who had received 3 grams of nicotinic acid per day for five years had serum uric acid levels greater than 8 mg/dl (normal 4-7 mg/dl). Seven percent of the drug group developed gouty arthritis. Hyperuricemia may be elicited by nicotinic acid, apparently through an increase in purine synthesis (Becker *et al* 1973) and reduced renal uric acid clearance (Gershon and Fox, 1974).
85. One case report describes a 41 year old male developing lactic acidosis induced by ingestion of sustained-release nicotinic acid (3 g/day) for one month for the treatment of type II hyperlipidemia (Earthman *et al* 1991).
86. Adverse ophthalmological effects have also been attributed to nicotinic acid therapy on rare occasions. These include blurred vision and cystoid macular oedema (Gass 1973, Millay *et al* 1988, Fraunfelder *et al* 1995, Callanan *et al* 1998), which are reversible on discontinuation of nicotinic acid therapy. However, re-institution of therapy is reported to be consistent with the recurrence of these effects (Gass, 1973).
87. Millay *et al* (1988) described three patients with nicotinic acid-induced cystoid maculopathy. All three patients had been taking high doses of nicotinic acid (3.0-4.5 g/day) prior to the onset of symptoms. Evaluation of an additional 15 asymptomatic patients, receiving high doses of oral nicotinic acid (1.0-6.0 g/day) for the treatment of hypercholesterolemia, revealed no evidence of cystic or other significant macular changes. Thus Millay and colleagues concluded that nicotinic acid causes a reversible toxic cystoid maculopathy in approximately 0.67% of patients taking high doses of the drug.
88. In a retrospective study of 190 patients taking medication for hyperlipidemia, conducted by Fraunfelder and associates (1995), those taking nicotinic acid were more likely ($p < 0.05$) to report blurred vision, eyelid oedema, and macular oedema compared with controls. Additionally, 7% of those taking nicotinic acid discontinued therapy due to

adverse ocular effects. The aetiology of the effect of nicotinic acid on the macula is unknown, although there is a theory of prostaglandin induced toxicity in müller cells (Fraunfelder *et al* 1995).

Chronic toxicity - nicotinamide

89. Patterson *et al* (1983) reported a case of severe liver injury occurring on two occasions in a patient taking self-prescribed nicotinic acid for the treatment of depression. The patient developed modest hepatotoxicity after taking nicotinic acid (4.5 g/day) for six months. This was followed by a much more severe episode of liver injury when he later reinstated nicotinic acid therapy and added 3 grams daily of nicotinamide. Liver biopsy revealed distortion of liver architecture, massive and submassive lobular collapse and marked cholestasis.
90. Administration of nicotinamide alone has also been reported to cause severe liver dysfunction following long-term, high dose (3-9 g/day) therapy. This case report describes a single patient who was taking fluphenazine enanthate and thiothixene hydrochloride prescribed for schizophrenia and was admitted to hospital for recurrent nausea and vomiting episodes. All medications were discontinued, except 2 to 3 g nicotinamide/day, the patient presented with two further episodes of nausea and vomiting. Toxicity was evident as parenchymal cell injury, portal fibrosis, and cholestasis. Nicotinamide was discontinued, the symptoms improved rapidly and all liver function tests returned to normal values in three weeks. It became apparent that the patient had increased the dose of nicotinamide to 9 g per day for several days before each previous episode of nausea and vomiting. With consent this scenario was recreated and similar symptoms were observed (Winter and Boyer, 1973).
91. Pelner (1946) describes an allergic type reaction to an oral dose of nicotinamide, described in a patient presenting with anaphylactic shock following an intravenous injection of nicotinic acid. It was later established by questioning that when nicotinamide tablets had been taken by mouth her lower lip had become swollen.

Reproductive toxicity

92. Doses of up to 2 g/day of nicotinic acid have been administered during pregnancy to supposedly niacin deficient women in developing countries, without evidence of foetal toxicity (Moghissi, 1981). Use of pharmacologic doses of nicotinic acid in pregnant or lactating women is not recommended since no studies have evaluated its safety in these settings.

Human Supplementation Studies

93. Several supplementation studies have been reported in which nicotinamide has been investigated to preserve β -cell function in Type I diabetics. These include the reports of Mendola *et al* (1989) who describe on a single-blind trial in twenty newly diagnosed Type I diabetics, who received 1 g/day for 45 days. Pozzilli *et al* (1995) describe a

double blind trial in a further 56 newly diagnosed Type I diabetics receiving 25 mg/kg bw/day for 12 months. No adverse effects were observed in either trial.

94. Similarly, Vague *et al* (1987) report no adverse effects in following a double-blind trial in 16 Type diabetics who received 3 g nicotinamide per day for six months. In a double-blind study in 35 newly diagnosed Type I diabetics, aged between 6 and 18 years individuals received 100 mg nicotinamide per year of age per day, up to a maximum of 1.5 g/day for 12 months. The authors report no significant adverse effects (Chase *et al* 1990).
95. The Deutsche Nicotinamide Intervention Study (DENIS), evaluated the clinical efficacy of high doses of nicotinamide in children at high risk of developing Type I diabetes. Fifty-five children were randomised into two groups and received either placebo or nicotinamide ($1.2 \text{ g.m}^{-2}.\text{day}^{-1}$) for a maximum duration of 3.8 years, mean treatment time was 2.1 years. Rates of diabetes onset was the same throughout the observation period in both groups. All biochemical (alanine aminotransferase, aspartate aminotransferase, bilirubin, blood sedimentation rate, γ -glutamyl transferase, urea, uric acid, creatinine and lactate dehydrogenase) were all in the normal range and means did not differ between the groups throughout the study (Lampeter *et al* 1998).
96. Currently underway is the European Nicotinamide Diabetes Intervention Trial (ENDIT), which will investigate the impact of daily oral administration of nicotinamide in first degree relatives of patients of Type I diabetics at increased risk of progressing to the disease. The proposed protocol is to use $1.2 \text{ g.m}^{-2}.\text{day}^{-1}$ of nicotinamide (corresponding to 2-3 g/day) for five years (Pociot *et al* 1993).
97. Hoffer (1969) reports from a personal communication that thirteen out of 262 patients given 3 g nicotinamide/day for 3 – 36 months, reported a range of adverse effects. These included headaches, heartburn, nausea, gastrointestinal disturbances, hives, fatigue and an inability to focus.

Adverse drug reactions

98. Suspected adverse reactions to medicinal products are reported to the Committee on Safety of Medicines/Medicines Control Agency. Many factors influence the number of reports received, and in most situations there is considerable “under-reporting” of reactions. Most of the adverse reactions reported for oral products containing nicotinamide or nicotinic acid relate to multiconstituent products, and may not, therefore, be directly attributable to the vitamin. Single constituent products are associated with a low number of suspected adverse reactions, with flushing reported most frequently.

Vulnerable Groups

99. Caution is advised when administering niacin to patients with a history of jaundice or liver disease, gallbladder disease, diabetes mellitus, gout, peptic ulcer, or allergy. Niacin is also contraindicated in patients with arterial haemorrhaging and severe hypotension (Figge *et al* 1988).

Animal toxicity

Acute toxicity – nicotinic acid

100. The L.D.₅₀ (subcutaneous) for nicotinic acid in the rat is 5.0 g/kg (Unna, 1939). For nicotinamide, the L.D.₅₀ (subcutaneous) in the rat is 1.68 g/kg (Brazda and Coulson 1946).
101. Chen and associates (1938) report toxicity following the administration of nicotinic acid (2 g/day) orally for less than 20 days in dogs. Symptoms included weight loss, bloody faeces, convulsions, and death with associated gastrointestinal (erosions) and central nervous system (shrunken ganglion cells of the cortex, hippocampus and basal ganglia) changes.
102. In a study conducted by Altschul and Hoffer (1958), no morphological or biochemical changes were observed in four young rats fed for 14 days on a balanced diet containing 2% nicotinic acid.

Sub-chronic toxicity – nicotinic acid

103. In a study conducted by Unna (1939), a group of 10 six week old rats received 1 gram of sodium nicotinate daily in their diet, over a period of 40 days. The animals showed no toxic symptoms and subsequent histological examination revealed no pathological changes.
104. Daily doses of 1 g/kg of sodium nicotinate were fed to three young dogs for over 63 days, with three littermates serving as controls. No toxicity was observed and growth was normal (Unna, 1939).
105. Chen *et al* (1938) administered nicotinic acid (1, 0.5, 0.2 and 0.06 g/day) orally to four dogs respectively for a period of 8 weeks. All four animals appeared in good health and gained weight. A trace of albumin and sugar was found in the urine of the dogs receiving the 1 g and 0.5 g doses.

Sub-chronic toxicity – nicotinamide

106. Nicotinamide was shown to strongly inhibit growth when administered to male Wistar rats, as 1 per cent of the basal diet, over a period of 28 days (Handler and Dann 1942).

Reproductive Toxicity – nicotinic acid

107. Replacement of chick egg white (2 ml) with a solution containing 20 mg of nicotinic acid at 2, 3 or 4 days of incubation resulted in embryos with a high incidence of neural tube closure defects, abnormal neural development, and abnormalities of the cardiovascular system (Hansborough 1947).

Reproductive Toxicity – nicotinamide

108. It is not known whether nicotinamide has teratogenic effects. In Wistar rats, 0.62 g/day of nicotinamide in the drinking water causes growth retardation. After 50 days on nicotinamide the mean weight of nicotinamide-treated rats was 72 per cent that of controls ($p < 0.01$). In contrast, the same dose of nicotinamide given to adult rats had no effect on weight over a period of four months (Petley and Wilkin 1992).

Carcinogenicity

109. When administered alone, for the entire life of the mouse, nicotinamide has no carcinogenic potency (Toth, 1983). However, combination of nicotinamide and streptozotocin, a naturally occurring nitrosourea, has been shown to cause islet cell tumours in male Holtzman rats (Rakieten *et al* 1971).

Genotoxicity

110. No evidence found.

Regulatory considerations

111. The Recommended Daily Allowance in the Food Labelling Regulations for niacin is 18 mg. The Infant Formula and Follow-on Formula Regulations (1995) recommend a minimum niacin content of 250 μg NE/100 kcal. The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations (1999) recommend a maximum niacin content of 9 mg NE/100 kcal. The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations (1997) recommend that whole diet products should provide 18 mg and meal replacements 6 mg. The Bread and Flour Regulations (1998) states that not less than 1.6 mg nicotinic acid or nicotinamide should be added to 100 g flour (as defined in the regulations).

Existing recommendations on maximum intake levels

112. The Committee on Medical Aspects of Food and Nutrition Policy reported that doses of nicotinic acid in excess of 200 mg causes vasodilatation of cutaneous blood vessels, and hence flushing. Very high doses of nicotinic acid (3-6 g/d) cause changes in liver ultra-structure and function (DH 1991).

Existing recommendations on maximum supplementation levels

113. The Council for Responsible Nutrition recommend levels of 450 and 1500 mg/day for long and short term supplementation with nicotinamide and 150 and 500 mg/day for long and short term supplementation with nicotinic acid (CRN, 1999).
114. In a report by a Department of Health/MAFF Working Group (1991) it was noted that niacin above the levels of 3-9 g (500 mg for sustained release niacin) was associated with adverse effects. It identified 500mg/day as an undesirable chronic dose, since it was uncertain whether the dose or formulation was the critical factor associated with liver damage and recommended that no daily dose should contain more than one tenth of this undesirable chronic dose ie 50 mg/day.

Summary

113. Niacin is a water-soluble vitamin that exists as nicotinic acid, nicotinamide and the coenzymes, NAD and NADP. Humans can synthesise niacin *de novo* from tryptophan and therefore, unless protein in the diet is restricted, niacin deficiency is rare. Meat, flour, eggs and milk are important sources of niacin in the diet. Cereals, corn and coffee also contain appreciable amounts of niacin, however, it is in a biologically unavailable form and requires processing, such as roasting or alkali-treatment, to be released.
114. Niacin is rapidly absorbed via the stomach and small intestine. Small doses are absorbed via carrier-mediated mechanisms, while larger doses, in excess of 3 grams, are almost completely absorbed via passive diffusion. Nicotinic acid is sequestered in erythrocytes and converted to nicotinamide, the main form of niacin in the bloodstream. Most tissues are capable of utilising either nicotinic acid or nicotinamide to synthesise the coenzyme NAD. Animal studies indicate that nicotinic acid is mainly concentrated in the liver and to a lesser extent in adipose tissue and kidney.
115. The excretion products formed are largely dependent on the form and dose of niacin ingested. The two main excretion products in urine are N-methylnicotinamide and N-methyl-2-pyridone-5-carboxamide. The ratio of these two excretory products is commonly used as an indication of niacin status.
116. The majority of human data available regarding nicotinic acid toxicity has been amassed from studies involving oral application of the drug to treat hypercholesterolemia. Symptoms of acute toxicity include flushing, nausea, vomiting, itching of the skin and gastrointestinal disturbances. Common features of chronic nicotinic acid toxicity include hyperglycemia, hyperuricemia,

hepatotoxicity and adverse ophthalmological effects. The sustained-release preparations of nicotinic acid are reported to be more hepatotoxic than the crystalline form. Limited data exists on the toxicity of nicotinamide since it is not used in the treatment of hypercholesterolemia.

117. No genotoxicity data for nicotinic acid or nicotinamide is available.
118. Nicotinamide alone is not carcinogenic, but co-administration with streptozotocin results in islet cell tumours. The potential teratogenic effects of nicotinic acid and nicotinamide are unknown, but nicotinamide has been shown to inhibit growth in rats.

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ANNEX 1 TO EVM/01/11

Tables referred to in the review

TABLE 1: NIACIN HUMAN TOXICITY DATA

Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	Reference
Human	<ul style="list-style-type: none"> • Hematemesis. • Elevated prothrombin time. • Abnormal liver function tests. 	6 g/day	6 grams	7 days	<ul style="list-style-type: none"> • Case report. • Self administration of nicotinic acid. 	Ferenchick & Rovner, 1989
Human	<ul style="list-style-type: none"> • One third to one half of patients had increased liver enzymes. • 44% had serum uric acid levels greater than 8 mg/dl. • 7% developed gouty arthritis. 	3 g/day	3 grams	54 months-6 years	<ul style="list-style-type: none"> • National collaborative study to investigate the use of niacin in coronary disease. • 1119 patients. • Men (30-64 years at entry). 	The Coronary Drug Project, 1975
Human	<ul style="list-style-type: none"> • 44% withdrew due to flushing, pruritus, nausea. • One report of hepatitis • One report of hypotension 	3 g/day	3 grams	12-30 months	<ul style="list-style-type: none"> • Double blind, placebo-controlled trial. • 25 patients. 	Hoeg <i>et al.</i>, 1984
Human	<ul style="list-style-type: none"> • Jaundice. • Cholestatic hepatitis. 	750 mg/day	750 mg	3 months	<ul style="list-style-type: none"> • Case report. • Nicotinic acid therapy for depression. 	Sugarman & Clark, 1974
Human	<ul style="list-style-type: none"> • Fulminant hepatic failure. • Stage III encephalopathy. 	3 g/day	3 grams	10 weeks	<ul style="list-style-type: none"> • Case report. • Nicotinic acid therapy for hypercholesterolemia. 	Clementz & Holmes, 1987

Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	Reference
Human	<ul style="list-style-type: none"> • Hypoalbuminemia • Oedema • Abnormal liver function tests 	3 g/day	3 grams	6 months	<ul style="list-style-type: none"> • Case report. 	Pardue, 1961
Human	<ul style="list-style-type: none"> • Marked jaundice. • Acute hepatitis with submassive necrosis. 	3 g/day	3 grams	2.5 years	<ul style="list-style-type: none"> • Case report. • Nicotinic acid therapy for psychological disturbance. 	Einstein <i>et al.</i>, 1975
Human	<ul style="list-style-type: none"> • Jaundice. • Itching. 	3 g/day	3 grams	1.5 years	<ul style="list-style-type: none"> • Case report. • Nicotinic acid therapy for hypercholesterolemia. 	Rivin, 1959
Human	<ul style="list-style-type: none"> • Increased sulfobromophthalein retention. • Increased liver enzymes. 	3-7.5 g/day	3 grams	13-32 months	<ul style="list-style-type: none"> • 10 Case reports. 	Parsons, 1961
Human	<ul style="list-style-type: none"> • Mild jaundice. • Massive and submassive lobular collapse. • Marked cholestasis. 	<ul style="list-style-type: none"> • 3 g/day (nicotinamide) • 4.5 g/day (nicotinic acid) 	4.5 g/day of nicotinic acid alone	18 months	<ul style="list-style-type: none"> • Case report. • Self-prescribed nicotinic acid for depression. 	Patterson <i>et al.</i>, 1983
Human	<ul style="list-style-type: none"> • Portal fibrosis. • Proliferated bile ducts. 	3 g/day	3 grams	18 months	<ul style="list-style-type: none"> • Case report. • Nicotinamide therapy for schizophrenia. 	Winter & Boyer, 1973

Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	Reference
Human	<ul style="list-style-type: none"> • Jaundice. • Nausea and vomiting. • Grade II encephalopathy. 	6 g/day	6 grams	3 days	<ul style="list-style-type: none"> • Case report • Substitution of long term crystalline nicotinic acid therapy with a sustained release preparation. 	Mullin <i>et al.</i>, 1989
Human	<ul style="list-style-type: none"> • Nausea and vomiting. • Elevated liver enzymes. • Stage IV hepatic encephalopathy. 	0.5 g/day	0.5 grams	2 months	<ul style="list-style-type: none"> • Case report. • Self-prescribed sustained release nicotinic acid therapy. 	Hodis, 1990
Human	<ul style="list-style-type: none"> • Elevated liver enzymes. • Nausea and vomiting. 	2-4 g/day	2 grams	7 days-2 months	<ul style="list-style-type: none"> • 3 case reports. • All prescribed sustained release nicotinic acid therapy 	Henkin <i>et al.</i>, 1990
Human	<ul style="list-style-type: none"> • 4/34 in the regular group experienced pruritus, increased liver enzymes and retinal oedema. • 4/31 in the time release group experienced nausea, dizziness, flushing and gastrointestinal symptoms. 	1.5-3.0 g/day	<ul style="list-style-type: none"> • 3 g/day (regular nicotinic acid) • 2 g/day (time release nicotinic acid) 	6 months	<ul style="list-style-type: none"> • Study investigating the effects of regular and time release nicotinic acid. • 71 patients, no controls 	Knopp <i>et al.</i>, 1985

Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	Reference
Human	<ul style="list-style-type: none"> 42% of the sustained release group developed dizziness, nausea and fatigue. 43% of the regular group developed flushing, elevated liver enzymes and retinal oedema. 	<ul style="list-style-type: none"> 0.1-5+ g/day (regular nicotinic acid) 0.1-3+ g/day (sustained release nicotinic acid) 	<ul style="list-style-type: none"> 0.1 g (regular nicotinic acid) 0.1 g (sustained release nicotinic acid) 	5 years	<ul style="list-style-type: none"> Investigative study into the effects of regular and sustained release nicotinic acid. 133 separate trials in 110 individuals, no controls 	Gibbons <i>et al.</i>, 1995
Human	<ul style="list-style-type: none"> 39% of the regular group developed fatigue and acanthosis nigricans. 78% of the sustained release group developed GI symptoms and elevated liver enzymes. 	<ul style="list-style-type: none"> 0.5-3 g/day (regular nicotinic acid) 0.5-3 g/day (sustained release nicotinic acid) 	0.5 grams	36 weeks	<ul style="list-style-type: none"> Randomised double blind study. 46 adults (23 assigned to each group) High dropout rate 	McKenney <i>et al.</i>, 1994
Human	<ul style="list-style-type: none"> Increased glycemia and glycosuria. Heightened requirement for insulin. 	1.0-3.0 g/day	1.0-1.5 grams	5-6 months	<ul style="list-style-type: none"> Study of the effect of nicotinic acid on 6 diabetic patients. 	Molnar <i>et al.</i>, 1964
Human	<ul style="list-style-type: none"> Polyuria ad polydypsia. Anorexia. Hyperglycemia. 	1.0-3.0 g/day	3 grams	7 months	<ul style="list-style-type: none"> Case study. 	Schwartz, 1993
Human	<ul style="list-style-type: none"> Epigastric pain. Activation of peptic ulcer. 	3.0-7.5 g/day	3 grams	130 weeks	<ul style="list-style-type: none"> 5 case studies. All patients had a history of ulcer symptoms. 	Parsons, 1960

Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	<i>Reference</i>
Human	<ul style="list-style-type: none"> • Nausea, weakness. • Lactic acidosis. 	3 g/day	3 grams	6 weeks	<ul style="list-style-type: none"> • Case study. • Patient had previously taken regular nicotinic acid for 1 year without incident. Switched to sustained release preparation. 	Earthman <i>et al.</i>, 1991
Human	<ul style="list-style-type: none"> • Cystoid macular oedema. 	1.5-5.0 g/day	1.5 grams	4-29 months	<ul style="list-style-type: none"> • 3 case studies. 	Gass, 1973
Human	<ul style="list-style-type: none"> • Reversible cystoid maculopathy in 0.67% of patients. 	1.0-6.0 g/kg	3 grams	3 months-5 years	<ul style="list-style-type: none"> • 3 case studies. • 15 asymptomatic patients. 	Millay <i>et al.</i>, 1988
Species	Endpoint/findings	Dose	LOAEL	Duration	Comment	<i>Reference</i>
Human	<ul style="list-style-type: none"> • Blurred vision. • Macular oedema. 	3.0-8.0 g/day	3 grams	1-36 months	<ul style="list-style-type: none"> • Retrospective survey of 102 patients. • 88 controls 	Fraunfelder <i>et al.</i>, 1995
Human	<ul style="list-style-type: none"> • Blurred vision, cystic appearance. • Cystoid macular oedema. • Mild metamorphopsia bilaterally. 	1.0-4.5 g/day	2 grams	1-18 months	<ul style="list-style-type: none"> • 3 case studies. 	Callanan <i>et al.</i>, 1998

ANNEX 2 TO EVM/01/11

INTAKES OF NIACIN EQUIVALENT¹ FROM FOOD AND SUPPLEMENTS

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

Total intakes of niacin equivalent

Table 1 provides information on the absolute intakes of niacin equivalent by the British population, from food sources and from all sources (including dietary supplements) classified by age and sex. Mean and median intake, and the upper and lower end of the intake distribution (defined as upper and lower 2.5 percentiles, respectively), are given. In addition, intakes of niacin equivalents from food and supplements for older people are presented both including and excluding prescribed niacin supplements, for comparison. Although these prescribed preparations were only taken by a small minority of participants within this group, intakes from them were found to have a disproportionate impact on mean daily intakes of niacin equivalent.

Average intakes of niacin equivalent were lowest for infants and highest for males aged 16-64 years. Average intakes increased significantly with age for pre-school children and young people aged 4-18 years, and decreased significantly with age for older people free-living in the community. Intakes from food sources were significantly lower in women under 35 years old compared with women aged 35 to 64 years. Dietary supplements made a significant contribution to average intakes for adult women and older women living in the community.

Mean niacin equivalent intakes from food were well above Reference Nutrient Intakes (RNIs) in all age/gender groups, and no more than 1% of any age/gender group had intakes below the Lower Reference Nutrient Intake (LRNI). Intakes from food and supplements

¹ Niacin is a generic term for compounds that have a common vitamin activity, and includes nicotinic acid and nicotinamide. 60mg of tryptophan can be taken as equivalent to 1mg of dietary niacin. Therefore niacin equivalent is the amount of preformed niacin + (1/60x tryptophan).

² Food and nutrient intakes of British infants. 1986

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

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

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

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

(including prescribed niacin) at the 97.5%ile were about 1.5 to 2 times the median in all groups.

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

Sources of niacin equivalent in the diet

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

The main food sources of niacin equivalents in this age group are cereals and cereal products and meat and meat products. Cereals and cereal products provided 33% of average intake, of which about a third each came from breakfast cereals and bread. Meat and meat products also provided 33%. Vegetables, potatoes and savoury snacks provided 12% of niacin equivalent intake, of which nearly a half came from potatoes.

UK legislation requires that not less than 1.60mg Niacin per 100g flour is added as a fortificant to all wheat flour except wholemeal flour. Some manufacturers voluntarily fortify breakfast cereals with niacin, to a level of around 15-18mg per 100g of product.

Infants obtained about a quarter of their niacin equivalent intake from milk and milk products, a further fifth from commercial infant foods and 19% from infant formulas. In all other age groups meat and meat products and cereals and cereal products were the major sources of niacin equivalent.

Niacin intakes from supplements

Dietary supplements containing niacin provided very little niacin for young people aged 4-18 years, contributing less than 1% of mean intake. In children aged 1½-4½ years, supplements contributed 2% to mean niacin intakes.

In adults, supplements provided 6% of mean intake of niacin equivalent for females and 2% for males. For older people free-living in the community dietary supplements provided 2% of intakes from all sources for men and 5% for women. For older people living in institutions the contribution was much smaller, 1% of mean intakes.

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

Table 4 shows the number of consumers of dietary supplements containing niacin in each age group, together with the mean, median and range of intakes from supplements for those who consumed them. No more than 8% of any group studied used supplements containing

niacin. In most cases these were multivitamin supplements. The range of intakes was wide with the maximum intake from this source at 600mg per day in females aged 16-64 years.

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

Table 1: Total intakes of Niacin

Age/sex	Absolute Niacin equivalent intake (mg/day) ⁷							
	Food Only				Food and Supplements			
	2.5% ile	Mean	Median	97.5% ile	2.5% ile	Mean	Median	97.5%ile
Infants (1986) 6-12mths/M&F	7.2 1.9**	12.5 5.5**	12.1 4.7**	20.9 12**	*	*	*	*
Pre-school children								
1½-2½ yrs/M/F	8.2	14.7	14.1	24.2	8.2	14.9	14.3	24.7
2½-3½ yrs/M/F	8.2	16.1	15.8	27.7	8.2	16.4	16.0	29.4
3½-4½ yrs/M	9.1	17.9	17.9	29.1	9.6	18.2	18.1	30.1
3½-4½ yrs/F	8.6	17.1	16.5	28.9	8.6	17.5	16.5	32.4
Young people (1997/8)								
4-6 yrs/M	11.6	22.8	22.0	35.9	11.6	22.9	22.0	38.3
4-6 yrs/F	11.6	20.4	19.9	33.3	11.6	20.7	20.2	33.3
7-10 yrs/M	16.1	26.0	25.6	40.5	16.1	26.1	25.6	42.2
7-10 yrs/F	13.7	23.4	23.0	35.3	13.7	23.6	23.0	35.8
11-14 yrs/M	13.6	30.0	29.8	47.0	13.6	30.0	29.8	47.0
11-14 yrs/F	13.7	24.6	23.8	40.5	13.7	24.8	24.0	40.7
15-18 yrs/M	19.4	36.6	35.0	57.5	19.4	36.8	35.0	60.9
15-18 yrs/F	12.8	25.2	25.0	42.4	12.8	25.6	25.0	44.9
Adults (1986/7)								
16-24 yrs/M	19.7	39.0	38.3	60.5	19.7	40.0	38.7	65.5
16-24 yrs/F	12.3	27.3	27.1	42.3	12.3	28.4	27.3	45.6
25-34 yrs/M	22.8	40.2	39.8	62.2	22.8	41.0	40.1	65.3
25-34 yrs/F	13.2	27.7	27.3	45.2	13.2	28.5	27.7	46.8
35-49 yrs/M	21.9	40.5	39.7	65.8	21.9	42.0	40.0	69.8
35-49 yrs/F	14.7	29.5	28.9	47.4	15.4	30.9	29.8	52.4
50-64 yrs/M	20.3	39.5	38.9	61.9	20.3	39.9	38.9	65.6
50-64 yrs/F	14.7	28.7	28.3	47.4	14.7	32.2	28.8	55.0
Older people free-living in the community (1994/5)								
65-74yrs/M	18.8	33.2	32.5	49.5	18.8(18.8)	33.9(33.8)	32.6(32.6)	54.7(53.4)
65-74yrs/F	12.7	25.7	25.4	41.2	14.0(14.0)	27.2(27.2)	26.0(26.0)	44.0(44.0)
75-84 yrs/M	15.7	30.1	29.3	45.4	15.7(15.7)	30.9(30.7)	29.9(29.7)	51.3(50.2)
75-84 yrs/F	12.4	24.0	23.6	37.6	13.0(13.0)	25.4(25.3)	23.8(23.8)	46.4(46.4)
85 and over/M	11.8	27.8	27.3	42.4	11.8(11.8)	28.9(28.6)	28.6(27.8)	52.7(49.6)
85 and over/F	9.8	22.0	21.6	37.2	9.8(9.8)	22.9(22.6)	22.4(22.3)	42.1(38.7)
Older people living in institutions (1994/5)								
65-84 yrs/M	12.7	27.4	27.2	41.7	12.7(12.7)	27.4(27.4)	27.2(27.2)	41.7(41.7)
65-84 yrs/F	11.4	24.8	24.0	37.8	11.8(11.8)	24.8(24.8)	24.1(24.0)	37.8(37.8)
85 and over/M	13.7	27.1	26.7	46.6	13.7(13.7)	27.5(27.2)	27.0(26.7)	47.8(46.6)
85 and over/F	11.9	22.1	21.0	35.5	11.9(11.9)	22.7(22.7)	21.5(21.5)	40.9(40.9)

* Data unavailable

** Figures are for preformed niacin

⁷ Data in brackets = intakes from food and supplements, excluding prescribed supplements

Table 2: Bodyweight adjusted Niacin equivalent intake

Age/sex	Bodyweight adjusted Niacin equivalent intake ($\mu\text{g}/\text{kg bwt}/\text{day}$) ⁸		
	<i>intakes from food and supplements</i> ⁹		
	Mean	Median	97.5%ile
Infants (1986) ¹⁰ 6-12mths/M&F	1.31	1.25	2.24
Pre-school children (1992/3) 1½-2½ yrs/M&F	1.23	1.16	2.09
2½-3½ yrs/M&F	1.12	1.09	1.91
3½-4½ yrs/M	1.10	1.09	1.78
3½-4½ yrs/F	1.07	1.04	1.98
Young people (1997/8) 4-6 yrs/M	1.09	1.04	1.70
4-6 yrs/F	1.02	0.99	1.58
7-10 yrs/M	0.88	0.84	1.41
7-10 yrs/F	0.76	0.74	1.31
11-14 yrs/M	0.67	0.65	1.11
11-14 yrs/F	0.53	0.52	0.90
15-18 yrs/M	0.56	0.54	0.90
15-18 yrs/F	0.44	0.43	0.77
Adults (1986/7) 16-24 yrs/M	0.58	0.57	0.98
16-24 yrs/F	0.48	0.47	0.80
25-34 yrs/M	0.55	0.54	0.83
25-34 yrs/F	0.47	0.45	0.84
35-49 yrs/M	0.55	0.53	0.93
35-49 yrs/F	0.49	0.47	0.91
50-64 yrs/M	0.52	0.51	0.87
50-64 yrs/F	0.51	0.45	0.91
Older people free-living in the community (1994/5) 65-74 yrs/M	0.44	0.43	0.70
65-74 yrs/F	0.42	0.39	0.72
75-84 yrs/M	0.42	0.41	0.68
75-84 yrs/F	0.40	0.37	0.80
85 and over/M	0.43	0.41	0.79
85 and over/F	0.39	0.38	0.72
Older people living in institutions (1994/5) 65-84 yrs/M	0.41	0.39	0.61
65-84 yrs/F	0.42	0.41	0.72
85 and over/M	0.41	0.39	0.71
85 and over/F	0.39	0.37	0.77

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

⁹ Data includes intakes from prescribed niacin supplements

¹⁰ Intakes for infants aged 6-12 months are from food only.

Table 3¹¹: Sources of Niacin equivalent in the diet

Food Type	Contribution of food types to average daily intake of niacin equivalent	
	mg/day	% of total
Cereal and cereal products	10.4	33
- of which breakfast cereals	4.1	13
- of which bread	3.5	11
Milk and milk products	2.5	8
Egg and egg dishes	0.4	1
Fat spreads	0	0
Meat and meat products	10.3	33
- of which chicken and turkey dishes	3.2	10
Fish and fish dishes	1.3	4
Vegetables, potatoes and savoury snacks	3.6	12
- of which potatoes	1.7	5
Fruits and nuts	0.3	1
Sugar, confectionery and preserves	0.4	1
Beverages	1.2	4
Miscellaneous	0.5	2
Total intake from food	31.1*	100*
<i>Intake from dietary supplements</i>	<i>0.3</i>	<i>1</i>
Total intake from food and supplements	31.4	100

*Total allows for rounding

¹¹ NDNS: young people aged 4-18 years. 1997/8. 15-18 year group

Table 4: Niacin intake from supplements¹²

<i>Age/sex</i>	Consumers of niacin supplements		Niacin equivalent intake from supplements (consumers only) (mg/day)		
	<i>Number</i>	<i>%</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>
<i>Infants (1986)</i> 6-12 mths/M&F	*	*	*	*	*
<i>Pre-school children (1992/3)</i> 1½-4½ yrs/M&F	70	4	6.5	5.0	0.7-18.0
<i>Young people (1997/8)</i> 4-6 yrs/M&F	9	3	8.5	10.4	0.0-15.0
7-10 yrs/M&F	10	2	8.3	8.6	0.0-15.0
11-14 yrs/M	2	<1	2.6	2.6	2.6
11-14 yrs/F	3	1	18.3	17.6	17.1-20.0
15-18 yrs/M	4	2	11.3	7.1	6.4-20.0
15-18 yrs/F	8	4	8.2	4.4	1.4-18.0
<i>Adults (1986/7)</i> 16-64 yrs/M	44	4	24.0	12.0	1.7-252.0
16-64 yrs/F	85	8	22.6	12.0	0.1-600.0
<i>Older people free-living in the community (1994/5)</i> 65 and over/M	35	6	15.0	18.0	1.1-40.0
65 and over/F	40	6	22.5	18.0	0.0-103.5
<i>Older people living in institutions (1994/5)</i> 65 and over/M	3	1	8.7	2.5	0.5-20.0
65 and over/F	6	3	8.8	1.7	0.7-38.5

* Data unavailable

¹² Data includes intakes from prescribed niacin supplements

ANNEX 3 TO EVM/01/11

Niacin: Summary table of selected nutrition related information and existing guidance on intakes

Unit of usage	mg niacin equivalent/1000kcal		mg /100 kcal	mg /100g
	male	female		
<i>UK DRV¹³ for adults (19-50+)</i>				
LRNI	4.4	4.4		
EAR	5.5	5.5		
RNI	6.6	6.6		
<i>Mean adult UK dietary intake</i>				
<i>From food (all sources)</i>				
Adults (16-64 years) ¹⁴	39.9 (40.9)	28.5 (30.3)		
Adults 65 years and over ¹⁵				
free living	32.0 (32.7)	24.8 (26.1)		
institutionalised	27.3 (27.3)	23.3 (23.6)		
EU labelling RDA ¹⁶	18mg			
Supplemental doses as nicotinamide	100 –250 mg			

¹³ Committee on Medical Aspects of Food and Nutrition Policy (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report on Health and Social Subjects 41. London: HMSO.

¹⁴ Dietary and nutritional survey of British adults. 1986/7

¹⁵ National Diet and Nutrition Survey of people aged 65 years and over. 1994/5

¹⁶ The Food Labelling Regulations 1996

Unit of usage	mg niacin equivalent/1000kcal	mg /100 kcal	mg /100g
Regulations Infant formula ¹⁷ Follow-on formula Cereal-based baby foods ¹⁸ Weight reduction ¹⁹ whole daily diet replacement meal replacement Bread and Flour Regulations ²⁰	18mg NE 6mg NE	Nicotinamide µg NE)* 250 Niacin (mg-NE) 0.8 NE - 9mg	Nicotinic acid and nicotinamide not less than 1.6
<i>Maximum total safe daily intake</i> COMA 1991 ¹ EHPM 1997 ²¹ Nicotinic Acid Nicotinamide	200 mg (nicotinic acid only) Long-term: Upper safe level: 500 mg Slow release upper safe level: 250 mg Short-term: Upper limit (short-term): 1,000mg Slow-release upper limit: 500mg Upper safe level (long-term): 1,500 mg Upper limit (short-term): 3,000 mg		

* NE = Niacin equivalent = mg nicotinic acid + mg tryptophan/60

¹⁷ The Infant Formula and Follow-on Formula Regulations 1995

¹⁸ The Processed Cereal-based Foods and Baby Foods for Infants and Young Children Regulations 1997.

¹⁹ The Foods Intended for Use in Energy Restricted Diets for Weight Reduction Regulations 1997.

²⁰ Bread and Flour Regulations 1998

²¹ Vitamins and Minerals A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers 1997.

