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Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Levels of Nicotinic Acid and Nicotinamide (Niacin)

(expressed on 17 April 2002)

B-1049 Bruxelles/Brussels - Belgium
Telephone: direct line (+32-2) 29 581.10/659.48/648.70, exchange 299.11.11. Fax: (+32-2) 299.48.91
Telex: COMEU B 21877. Telegraphic address: COMEUR Brussels.

http://europa.eu.int/comm/food/fs/sc/scf/index_en.html

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FOREWORD

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

1. INTRODUCTION

Niacin is the term used to describe two related compounds, nicotinic acid and nicotinamide, both of which have biological activity. Niacin is not strictly speaking a vitamin because it is formed from the metabolism of tryptophan, and is not *per se* essential to the body, providing that there is an adequate supply of the essential amino acid tryptophan (Horwitt *et al.*, 1981). Niacin is the precursor for two cofactors, NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate), which are essential for the functioning of a wide range of enzymes involved in redox reactions.

The condition that is characteristic of a deficiency of both tryptophan and preformed niacin is pellagra, which was originally recognised in 1735 and is characterised by spinal pains, “magenta tongue”, digestive disturbances and subsequently erythema with drying and expurgation of the skin. Various nervous manifestations, such as spasms, ataxic paraplegia and mental disturbances occur in severe cases. The deficiency disease occurred in Italy, Southern France, Spain and in the southern states of the United States of America where over 170,000 cases were reported annually between 1910 and 1935. In the 1930s the recognition of the essential role of nicotinic acid in relation to a related condition, canine black-tongue, and the essential role of nicotinamide in the cofactors NAD and NADPH led to the recognition of the nature of the deficiency, and the establishment of niacin as a vitamin (Smith *et al.*, 1937). Short-term (3 weeks) niacin deficiency in the elderly may lead to an increase in serum triglycerides in some subjects (Ribaya-Mercado *et al.*, 1997).

2. NUTRITIONAL BACKGROUND, FUNCTION, METABOLISM AND INTAKE

The co-enzymes NAD and NADPH are involved in a large number of redox reactions essential for the normal functioning of mammalian cells. In addition, NAD is the source for ADP-ribose, which is used in repairing DNA breakage caused by mutagens and other toxins.

Niacin is present in food largely as bound forms that require hydrolysis to release the free nicotinamide or nicotinic acid prior to absorption. In animal tissues niacin is present mainly as the coenzymes NAD and NADP (Henderson, 1983; Turner and Hughes, 1962). There are

negligible concentrations of free nicotinic acid in crops such as cereals. Boiling releases most of the total niacin present in sweet corn as nicotinamide (up to 55 mg/kg) but very little as nicotinic acid (<5 mg/kg) (Kodicek *et al.*, 1974; Mason *et al.*, 1973). The niacin in cereals such as wheat, barley and oats does not give free nicotinic acid or nicotinamide on cooking (Mason *et al.*, 1973). Roasted coffee contains higher concentrations of free nicotinic acid (160-400 mg/kg) (Smith, 1963).

Nicotinamide may be obtained from the diet where it is present primarily as NAD and NADP, which are hydrolysed in the intestine and the resulting nicotinamide absorbed either as such, or following its hydrolysis to nicotinic acid. In addition, the niacin in cereals is present as a glycoside of nicotinic acid, which undergoes limited hydrolysis *in vivo* and is essentially not absorbed from the gastrointestinal tract and is not bioavailable (Yu and Kies, 1993). Nicotinic acid itself is rapidly absorbed from both the stomach and the upper small intestine (Bechgaard and Jespersen, 1977). The conversion of nicotinic acid to nicotinamide occurs subsequent to its formation as a pyridine nucleotide; nicotinic acid reacts with 5-phosphoribosyl-1-pyrophosphate to form the nicotinic acid mononucleotide, which then condenses with ATP to form the nicotinic acid analogue of NAD, which is subsequently converted to NAD by a reaction with glutamine and ATP. In contrast, nicotinamide is converted to the pyridine nucleotide simply by reaction with phosphoribosyl-1-pyrophosphate. The cofactor NAD is converted to NADP by reaction with ATP. Nicotinamide can be formed from NAD via enzymatic cleavage to nicotinamide and adenosine diphosphate ribose.

The major pathway of metabolism of nicotinamide is by methylation in the liver to form N^1-methyl nicotinamide via reaction with methionine (as a methyl donor) and ATP. N-Methyl nicotinamide does not have biological activity and is a polar, water-soluble excretory product. It may be further oxidised in the 6 position of the pyridine ring to give N^1-methyl-6-pyridone-3-carboxamide. High doses of nicotinic acid are excreted in the urine, as nicotinic acid and its glycine conjugate (nicotinuric acid) (Figge *et al.*, 1988; Stern *et al.*, 1992).

Because of the metabolic formation of niacin from tryptophan, the dietary requirements for niacin are complex and related to the dietary content of both tryptophan and niacin (neglecting niacin in cereals, which is largely not bioavailable). By convention the total niacin equivalents in the diet is taken as the sum of preformed niacin plus 1/60 of the tryptophan content (Horwitt *et al.*, 1981; SCF, 1993). There is no absolute requirement for preformed niacin in the diet, and the 1993 SCF evaluation recommended intakes of niacin equivalents between 9 and 18 mg/day. However, the SCF report stated "it is likely there is no requirement for any preformed niacin in the diet under normal conditions and that endogenous synthesis from tryptophan will meet requirements".

Intake data are available for a number of European countries (Table 1), which indicate that average intakes are about twice those recommended in the 1993 report of the SCF. The data also show that food supplements (that contain nicotinamide) represent a minor source of intake, even at the 97.5^{th} percentile of intake.

Table 1. The daily intakes of niacin equivalents in EU countries (mg/day)

	Population	n	Method	Supplements*	Mean or Median	97.5%
Austria[a]	individual	2488	24h recall	Not defined	30.6	66.3
Germany[b]	men	856			15.0	28.8
	women				11.6	20.5
Germany[c]	men	1138		-	39.2	
	women	1268		-	27.8	
	men	1540		+	39.5	
	women	240		+	27.8	
		347				
Italy[d]	Household	2734	7-day record	+	19	31
Netherlands[e]	Household	5958	2-day record	-	16.7	36.7
UK[f]	men	1087	7-day record	-	39.9	62.2
	women	1110		-	28.5	46.4
	men	1087		+	40.9	67.4
	women	1110		+	30.3	51.2
Ireland[g]	men		7-day record	-	27.1	46.7
	women			-	18.6	32.3
	men			+	28.2	60.0
	women			+	20.7	44.0

Results are for intake as preformed niacin and from metabolism of dietary tryptophan.
* + data included supplements; - data excluded supplements.
[a] Elmadfa *et al.* (1998)
[b] Heseker *et al.* (1992)
[c] Mensink and Ströbel (1999)
[d] Turrini (INRAN)
[e] Hulshof (1999) (preformed only)
[f] Gregory J *et al.* (1990)
[g] IUNA (2001) (preformed only)

3. HAZARD IDENTIFICATION

All of the available data on hazard identification and characterisation relate to studies following the administration of either nicotinic acid or nicotinamide.

3.1 Data from studies in animals

There is a very limited animal toxicity database on either nicotinic acid or nicotinamide, with the majority of the available studies published before 1960. Weight loss, convulsions and death were reported in dogs given nicotinic acid at 2 g per day for 20 days, but not in dogs treated with up to 1 g per day for 8 weeks (Chen *et al.*, 1938), or in dogs given sodium nicotinate at a dose of 1 g per kg body weight for 63 days (Unna, 1939). Toxicity was not found in rats given 1 g per day of sodium nicotinate in the diet for 40 days (Unna, 1939), whereas nicotinamide inhibited the growth of rats when given at 1% in the diet for 28 days (Handler and Dann, 1942). Suppression of growth in rats was reported when nicotinamide was incorporated into the drinking water to give an intake of 0.62 g/day (Petley and Wilkin, 1992). A study has reported that nicotinamide was not carcinogenic when mice were given a 1% nicotinamide solution as drinking water for their life-span (Toth, 1983). Data on genotoxicity have not been identified.

Niacin deficiency results in birth defects (Chamberlain and Nelson, 1963) and impaired viability; nicotinamide is transferred actively across the placenta (Hill and Longo, 1980; Kaminetzky *et al.*, 1974) and into breast milk (Deodhar *et al.*, 1964). However there are only limited data on the effects of excessive niacin either *in utero* or during neonatal development. Abnormal neural tube closure defects and other abnormalities were reported when chick egg white was replaced with a solution containing 20 mg of nicotinic acid (Hansborough, 1974) but such experiments are not of value for hazard identification. The limited data available from animal studies did not indicate that either nicotinamide or nicotinic acid was teratogenic, but these were observations from old studies (cited in Schardein, 2000) that would not be considered adequate for risk assessment purposes.

3.2 Data from studies in humans

The principal identification of hazards associated with excessive intakes of niacin have arisen from studies in which high doses of nicotinic acid have been used for its therapeutic effects in lowering blood cholesterol and blood hyperlipidaemias. The most comprehensive study was that conducted by the Coronary Drug Project Research Group (1975). A number of hazards have been reported to be associated with high doses of nicotinic acid. These have been summarised by the US National Academy of Sciences Institute of Medicine in their evaluation of dietary reference intakes.

In addition, nicotinamide has been investigated as a method for reducing the risk of the development of diabetes (Knip *et al.*, 2000). Studies have shown that nicotinamide can afford protection in an animal model of immune mediated insulin-dependent diabetes (Reddy *et al.*, 1990), and it has been investigated in a number of clinical trials, some of which are still ongoing.

3.2.1 Vasodilatory effects (flushing)

Vasodilation is commonly seen in patients given high doses of nicotinic acid for the treatment of hyperlipidaemias. Very large single doses cause hypotension, although tolerance develops to this effect after several days of continued high dose intake. In general, flushing is a mild and transient effect although in many clinical trials it has resulted in patients withdrawing from treatment. The flushing activity appears to be related to the presence of a carboxyl group on the pyridine nucleus since compounds lacking this function, including nicotinamide, are not associated with facial flushing (Bean and Spies, 1940). Flushing is associated with periods of rapid rises in blood concentrations, and sustained-release formulations were developed for the use of nicotinic acid in the treatment of hypercholesterolaemia, in order to minimise this side-effect. Flushing is produced via prostaglandin D_2 release (Morrow *et al.*, 1989 and 1992) and a "niacin flush-test" has been used as a method of investigating essential fatty acid metabolism (Glen *et al.*, 1996). Tolerance develops due to decreased formation of prostaglandin D_2 on repeated dosage (Stern *et al.*, 1991). Although flushing is not a clearly adverse effect and single oral doses of 100 mg do not alter heart rate or blood pressure, some patients in the study of Spies *et al.* (1938) reported dizziness after oral nicotinic acid (doses not defined). Theoretically if flushing occurred in the elderly, it could exacerbate mild postural hypotension, and could increase the risk of falls, which are a common cause of morbidity in the elderly. This risk relates to taking supplements containing nicotinic acid (not nicotinamide), especially if taken on an empty stomach.

3.2.2 Gastrointestinal effects

Gastrointestinal effects such as dyspepsia, diarrhoea and constipation are common in patients with hypercholesterolaemia given high doses of nicotinic acid (3 g/day - especially as the sustained-release formulation; Knopp *et al.*, 1985).

3.2.3 Hepatotoxicity

Severe and potentially life-threatening hepatotoxicity has been associated with treatment of patients with 3-9 g nicotinic acid per day for periods of months or years for the treatment of hypercholesterolaemia. Severe cases show liver dysfunction and fulminant hepatitis and may even proceed to encephalopathy requiring liver transplantation. Many of the patients showing hepatotoxicity were taking the slow release formulation of the compound, so that in contrast to the flushing discussed above, the development of hepatic toxicity is a function of long-term chronic exposure to relatively constant levels rather than the fluctuating levels and rapid rises which produce flushing.

3.2.4 Glucose intolerance

Nicotinic acid (3 g/day) has been reported to impair glucose tolerance in otherwise healthy individuals treated for hypercholesterolaemia.

3.2.5 Other effects

There have been rare reported cases of a range of effects including blurred vision, macular oedema and increased plasma homocysteine concentrations in patients given high doses of nicotinic acid. These effects were reported at doses similar to those producing hepatic dysfunction, and were reversible upon cessation of high dose treatment. (See below).

There has been a single report of a possible association with congenital malformation in women taking nicotinamide during early pregnancy (Nelson and Forfar, 1971). On the basis of their retrospective survey of drug and vitamin prescriptions during pregnancy in 1369 mothers, the authors reported that a significantly ($P<0.05$) higher proportion of women with infants showing abnormalities took nicotinamide in the first 56 days (5/458), compared with mothers of normal babies (1/911). In contrast no such relationship was found during later phases of pregnancy or over the whole of the pregnancy. The paper did not report the doses of nicotinamide taken. This finding is in contrast to the results of the large multicentre study on vitamins and the prevention of neural tube defect (MRC Vitamin Study Research Group, 1991). In that study 1817 women with high risk for producing a baby with neural tube defect were randomised into 4 groups; one group received folic acid, one group a multivitamin preparation (that did not include folate but contained 15 mg/day of nicotinamide), one group was given both preparations and one group received neither preparation. Although the study focussed on neural tube defects, any foetal malformation was recorded together with other pregnancy outcomes, and there was no difference in incidence between the multivitamin preparation and placebo.

4. DOSE-RESPONSE ASSESSMENT

4.1 Nicotinic acid

4.1.1 Vasodilatory effects (flushing)

Low doses of nicotinic acid may produce mild but noticeable flushing when taken on an empty stomach (Hathcock, 1997) and this represents the adverse effect detected at the lowest doses. An early study (Smith *et al.*, 1937) reported that a single oral dose of 60 mg nicotinic acid produced marked flushing, which was not associated with changes in heart rate or blood pressure. Spies *et al.* (1938) reported flushing in 5% and about 50% of subjects given single oral doses of 50 mg and 100 mg nicotinic acid, respectively. The dose-response for flushing was examined further by Sebrell and Butler (1938) who gave 3 groups of 6 subjects daily dose of 10, 30 or 50 mg nicotinic acid for 92 days as single oral doses given in solution added to tomato juice and consumed with the mid-day meal; flushing was reported intermittently by 4, 2 and 0 of the subjects given 50, 30 and 10 mg, respectively. The response is possibly related to periods of rapid increase in plasma concentrations of nicotinic acid, because the response is greater after intravenous dosage and is blunted if taken orally with food (Bean and Spies, 1940). Rash, pruritus and a sensation of warmth was reported following the consumption of pumpernickel bagels, accidentally made to contain 190 mg nicotinic acid per bagel (MMWR, 1983) and following the consumption of cooked meat containing 225 mg/100 g (Press and Yeager, 1962). This hazard does not seem to be related to nicotinamide. The facial flushing associated with low doses of nicotinic acid can be prevented by co-administration of an inhibitor of prostaglandin synthesis such as aspirin (although this is not always recommended - Schuna, 1997).

4.1.2 Gastrointestinal effects

Gastrointestinal effects such as dyspepsia, diarrhoea and constipation are common in patients given high doses of nicotinic acid for hypercholesterolaemia. Ruffin (cited in Sebrell and Butler, 1938) reported nausea and vomiting in 2 out of 10 subjects given 1 g of nicotinic acid. Spies *et al.* (1938) reported nausea and vomiting in subjects given oral doses of 300-1500 mg of nicotinic acid. Nausea is a common adverse effect in the studies of patients given 3 g of nicotinic acid daily for hypercholesterolaemia.

4.1.3 Hepatotoxicity

The first report of hepatotoxicity associated with the administration of nicotinic acid was in a study in dogs (Chen *et al.,* 1938), which compared the toxicity of nicotine with nicotinic acid. In that study 2 dogs were given either 145 or 133 mg/kg bw/day nicotinic acid orally and both developed convulsions and excreted blood in their faeces about 2-3 weeks after treatment started. *Post mortem* observations included gastrointestinal adhesions, “fatty metamorphosis” of the liver and neuronal damage.

The first case-report of hepatotoxicity of nicotinic acid in humans was in a 23 year old man who developed jaundice after taking 3 g per day for 72 weeks (Rivin, 1959). Subsequent case-reports included a man who had taken 3 g per day for 6 months (Pardue, 1961), and a woman who developed pruritus and jaundice after taking 3 g nicotinic acid (together with 3 g vitamin C and 100 mg pyridoxine for a psychological disturbance) per day for 2.5 years (Einstein *et al.*, 1975). A survey of 66 patients treated with nicotinic acid, of whom 51 had taken 3 g/day for 12 months or more, found a high incidence of abnormal liver function tests (23 patients)

while on treatment, with 2 patients developing jaundice (Berge *et al.*, 1961).

Approximately one-third of the 1119 patients in the study of the Coronary Drug Project Research Group (1975), who received 3 g/day nicotinic acid for up to 5 years, were reported to have elevated serum glutamate-oxaloacetate transaminase (SGOT) and alkaline phosphatase levels. There have been a number of reports of individual cases of patients with severe hepatotoxicity resulting from the use of nicotinic acid for hypercholesterolaemia or hypertriglyceridaemia. Four cases of liver disease were associated with doses of 2.5 g of sustained-release nicotinic acid daily for 5 months, 1.5 g of sustained-release nicotinic acid per day for 3 months, 2.25 g of sustained-release nicotinic acid per day for an unrecorded period, and 2 g of sustained-release nicotinic acid daily for an unrecorded period (Coppola *et al.*, 1994). In all cases, cessation of nicotinic acid administration resulted in resolution of the liver symptomatology. A single case report gave some insight into the dose-response relationship for sustained-release nicotinic acid since symptoms of anorexia, fatigue and persistent nausea arose approximately one month at the end of a sequence of dose escalation from 1 g/day through 3 g/day for one month and finally 4 g/day for one month (Lawrence, 1993). A rapid reversal of the symptoms was found at 3 weeks after discontinuation of the nicotinic acid therapy.

Rader *et al.* (1992) reviewed the available cases of hepatotoxicity and side-effects from conventional and sustained-release nicotinic acid and concluded that adverse effects were frequently seen shortly after an abrupt change from unmodified to sustained-release preparations. Their paper summarised both the dose and the duration of therapy in the different cases of hepatic toxicity and showed that in general toxicity was associated with doses of 3 g/day or more, although there were 2 cases who took less than 1 g/day for short periods (0.75 g conventional nicotinic acid per day for less than 3 months; 0.5 g sustained-release nicotinic acid for 2 months).

A comparison of an immediate release formulation and a sustained-release formulation of nicotinic acid in two groups of 23 patients with low density lipoproteinaemia studied the sequential effect of 0.5, 1, 1.5, 2 and 3 g per day for period of 6 weeks each. The therapeutic efficacy was similar for the two formulations but there were interesting differences in the side-effect profiles. About 39% of subjects on the immediate release formulation withdrew before completing the 3 g/day dose due to vasodilatory symptoms and fatigue, whereas 78% of subjects in the sustained-release group withdrew before completion of the study, primarily due to gastrointestinal tract symptoms, fatigue and changes in serum aminotransferases, indicative of hepatic dysfunction. Interestingly, the lowest dose of 0.5 g/day appeared to be better tolerated with the sustained-release preparation than the immediate release primarily because of vasodilatory symptoms (McKenney *et al.*, 1994).

The study of McKenney *et al.* has been criticised because the dosage regimen of twice daily administration was considered to minimise the tolerability of the protocol and give the greatest potential for side-effects. The authors of the critique (Kennan *et al.,* 1994) report that there was only a 5% drop-out rate as a result of intolerance and toxicity after one year in a study of 1119 subjects receiving 3 g (1 g three times a day) of immediate release nicotinic acid. The study of McKenney *et al.* was also criticised because of the high top dose administered since drop-out rates of only 3-4% had been reported in studies where the maximum dose was 2 g/day.

The results of a multicentre study on the long-term safety and efficacy of a sustained-release preparation of nicotinic acid were reported by Guyton *et al.* (1998). Nicotinic acid doses,

ranging from 0.5-3 g were given once a day at bedtime to a total of 269 patients for a period up to 96 weeks. The average dose given at the end of the study was 2 g/day with a range from 1-3 g, which indicates the poor tolerability of doses greater than 2 g/day. The principal adverse effect was flushing which resulted in 4.8% of the participants discontinuing the study (although they were advised that they could take aspirin to reduce this symptom). Those individuals who showed flushing had an average of one episode of 1.2 hours duration every 4-5 weeks. A total of 9 patients showed elevated transaminase levels of at least 2 times the upper limit of normal. However 5 of these patients were on a combination therapy including nicotinic acid plus nystatin or a bile acid sequestrant. In 5 of the cases the transaminase elevation resolved while treatment with nicotinic acid continued and without a reduction in dose. Therefore this study demonstrates only mild hepatotoxicity in a group of subjects given controlled doses of sustained-release nicotinic acid.

Dalton and Berry (1992) describe a single case of a woman who presented with hepatotoxicity after taking crystalline nicotinic acid for a period of 2 years and sustained-release formulation for a period of only 2 days prior to admission. Her symptoms on admission to hospital included hypothermia, hypotension and metabolic acidosis, and the authors suggested that this may have been a result of the change from conventional to sustained-release nicotinic acid associated with prolonged flushing and possibly significant transcutaneous heat loss. This observation is ironic, since the sustained-release formulation was primarily developed to minimise the skin flushing reaction associated with conventional nicotinic acid (Rader *et al.*, 1992). Some studies have suggested that sustained-release formulations of nicotinic acid produce a greater incidence of hepatotoxicity (Christensen *et al.*, 1961; Knopp, 1989; Mullin *et al.*, 1989; Henkin *et al.*, 1990), although this is not a consistent observation in all studies (Gibbons *et al.*, 1995).

Gray *et al.* (1994) reported that the daily intakes of nicotinic acid in 42 elderly diabetic patients who developed hepatic dysfunction (2.33 ± 0.15 g/day) were significantly higher than the doses for the remaining 854 subjects (1.64 ± 0.03 g/day) who did not develop hepatic dysfunction.

Effects on prothrombin time have been reported in patients taking sufficient nicotinic acid to cause hepatic toxicity. Elevated prothrombin times have been reported in a small number of cases, which were associated with only mild elevation of transaminase levels so that blood-clotting disorders may become the limiting sign of hepatotoxicity in some cases. Three cases reported by Dearing *et al.* (1992) were receiving 2.0, 2.0 and 3.0 g of nicotinic acid daily.

In contrast to the studies that have reported abnormal liver function in patients treated with nicotinic acid, a small study in the group of 30 patients with hyperlipidaemia who were given slow release nicotinic acid at 1 g/day for 2 months and then 2-3 g/day for 10 months reported a low incidence of symptoms other than skin flushing (which had an incidence of 26.7% - mostly at the start of the treatment period). There was no evidence of hepatic abnormalities as indicated by changes in serum aminotransferases, alkaline phosphatase or antipyrine test results (Chojnowska-Jezierska and Adamska-Dyniewska, 1998).

A large number of studies have defined the efficacy and tolerability of both conventional and sustained- or controlled-release nicotinic acid in the treatment of hypercholesterolaemia and hyperlipidaemias. The data from these studies provide adequate evidence of the hazard identification and some evidence of dose-response characterisation. A major problem with the use of such data for establishing an upper level is that the doses investigated were restricted to those that showed clinical efficacy in the conditions being treated (mostly 3 g/day), and there

are few data available at lower levels (Rader *et al.*, 1992). Hodis (1990) reported a case of acute hepatic failure, which was ascribed to treatment with 500 mg per day nicotinic acid, however there was no repeat challenge or other data to support causation (other than an absence of other recognised reasons).

4.1.4 Glucose intolerance

Although hyperglycaemia is a relatively rare side-effect associated with high doses of nicotinic acid, it can be of clinical significance. Administration of 3 g of nicotinic acid per day for 10-14 days to volunteers resulted in an increase in fasting blood glucose and immuno-reactive insulin in serum (Miettinen *et al.*, 1969). An increase in blood glucose concentrations, glycosuria, elevated serum ketone bodies, and an increase requirement for hypoglycaemic medication were reported in 6 patients with diabetes mellitus, who were receiving between 1 g and 3 g of nicotinic acid daily for a period of 2 weeks or more (Molnar *et al.*, 1964). Gray *et al.* (1994) reported a high incidence of hyperglycaemia in elderly hyperlipidaemic patients who had been treated with high doses of nicotinic acid (average dose 1.7 g/day). Schwartz (1993) described a patient who was hospitalised with severe hyperglycaemia following treatment with 3 g of nicotinic acid per day for 4 months; administration of insulin and oral hypoglycaemics reversed and stabilised the blood glucose levels.

4.1.5 Other effects and overall dose-response relationships

Thrombocytopaenia, which resolved on cessation of nicotinic acid treatment, was reported in a single patient who developed hepatitis 10 years after the initiation of nicotinic acid treatment (Reimund and Ramos, 1994).

The plasma concentrations of homocysteine were increased by 55% in patients with peripheral arterial disease who were treated with nicotinic acid (Garg *et al.*, 1999). The 52 patients were a subgroup from a multicentre study in which patients were given increasing doses of 100, 500 and 1000 mg per day over periods of 3-4 weeks (in order to identify patients who tolerated nicotinic acid), following which the subjects were randomised to receive either placebo or nicotinic acid (up to 3 g per day). The plasma concentrations of homocysteine were measured at baseline, at randomisation and at 18 and 48 weeks after randomisation. Plasma homocysteine increased from 13.1 ± 0.5 μM at baseline to 15.3 ± 0.8 μM at randomisation. After randomisation the levels increased further in those receiving nicotinic acid (to about 20 μM at 18 and 48 weeks; n=25 and 24, respectively), but decreased in those on placebo (to about 12 μM at 18 and 48 weeks; n=21 and 22, respectively). The clinical significance of this is unclear, but elevated plasma homocysteine is a recognised risk factor for coronary artery disease.

Severe reversible cystoid macular oedema was reported in 3 patients receiving high-doses of nicotinic acid (Gass, 1973). A survey of 116 patients who had received nicotinic acid (3 g or more per day) for treatment of hyperlipidaemia and a similar number of patients who were not treated with nicotinic acid revealed an increased incidence of decreased vision associated with sicca syndromes, eyelid oedema or macular oedema (Fraunfelder *et al.*, 1995).

Because the majority of the data arise from studies designed to investigate the hypolipidaemic action of nicotinic acid, most of the data relate to doses of 1 g/day or more. In consequence, there are few data available on the tolerability and toxicity of doses less than 500 mg/day. In general the main adverse effect reported at intakes below the 500 mg/day has been flushing

which is generally self-limiting in relation to continuation of treatment or intake of nicotinic acid.

High dose nicotinic acid (0.5-2.25 g daily) has been used for the treatment of severe hypercholesterolaemia in children. A retrospective review of 21 such cases reported similar adverse effects to those found in adults, with 6 children showing reversible dose-related elevations in serum transaminases, and 8 children who discontinued treatment because of flushing, abdominal pains and/or elevated serum transaminase levels. Hepatitis was reported in subjects with very high doses on a mg/kg bw/day basis (50, 67, 41, 34, 48 and 39 mg/kg bw/day) (Colletti *et al.*, 1993).

In a study in the USA on elderly male veterans (age 62 ± 9 years) the doses administered averaged 1.7 g/day with a mean duration of intake of 13 ± 10 months (Gray *et al.,* 1994). Almost one-half of the subjects discontinued treatment because of adverse effects with poor glycaemic control occurring in 41% of patients with diabetes mellitus. Probable and possible nicotinic acid-induced hepatotoxicity occurred in 2.2 and 4.7% of the patient group. These data indicate that the spectrum of toxicity is similar in elderly and young adults.

The side-effect profile of wax matrix sustained-release nicotinic acid was studied in groups of younger (<50 years) and older (50-70 year old) hypercholesterolaemic subjects. The study was a randomised double-blind placebo controlled design of 8 weeks duration with doses of 1.0-2.0 g/day. Clinically significant side-effect included flushing, itching, tingling, upper gastrointestinal symptoms, constipation, diarrhoea, dizziness, palpitations and blurred vision; the overall incidence of adverse effects was similar in the two difference age groups (Keenan *et al.,* 1992).

4.2 Nicotinamide

4.2.1 Vasodilatory effects (flushing)

The flushing reported with nicotinic acid does not occur following nicotinamide, either given as an intravenous injection (Bean and Spies, 1940) or when it is given orally at high-doses to patients with diabetes (Knip *et al.*, 2000).

4.2.2 Gastrointestinal effects

Gastrointestinal effects are rare following high-dose treatment with nicotinamide (Knip *et al.*, 2000). Nausea was reported in a single subject who had taken nicotinamide 3 g daily followed by 9 g per day for several days (Winter and Boyer, 1973).

4.2.3 Hepatotoxicity

Only one patient has been reported to have developed hepatitis after nicotinamide alone, and this subject had been given 3 g daily followed by 9 g per day for several days (Winter and Boyer, 1973); other subjects who developed liver disease after nicotinamide had also received prolonged treatment with nicotinic acid (see Rader *et al.*, 1992).

Increased serum transaminase levels were reported for 17 out of 41 children with attention deficit disorders treated for 12 weeks with daily doses of 3 g nicotinamide, in combination with 1.2 g pantothenic acid, 3 g ascorbic acid and 0.6 g pyridoxine (Haslam *et al.*, 1984). Whether this hepatotoxic effect was related to the high dose of nicotinamide, or to the

combination with the high doses of pantothenic acid, vitamin C and pyridoxine, cannot be concluded from this study, and therefore, this study cannot be used in risk assessment of nicotinamide.

The supplementation trials on the use of nicotinamide to prevent or delay the development of diabetes mellitus have not reported hepatitis as an adverse effect (Knip *et al.*, 2000); however these have involved smaller number of subjects, have been of shorter duration and at lower doses than the trials on the use of nicotinic acid for the treatment of hypercholesterolaemia. Ten newly diagnosed Type 1 diabetic patients were given 1 g/day for 45 days (Mendola *et al.*, 1989), and compared over the following year with a group who were treated with placebo; the authors reported that no adverse effects were observed when physical, biochemical and haematological parameters were considered (no details of the tests were given and the main aim of the paper was to study efficacy). A group of 35 patients, aged 6 to 18 years, were given either placebo (n=17), or up to 1.5 g/day of slow-release nicotinamide (n=18) for 12 months (Chase *et al.*, 1990); various tests, including measurement of serum transaminases, alkaline phosphatase and bilirubin, were performed after 4 and 12 months, and remained normal in all subjects. No adverse effects were reported in a group of nine Type 1 diabetic patients with ketosis given 3 g of nicotinamide per day, three of whom were treated for up to 12 months, compared to 7 similar patients given placebo (Vague *et al.*, 1987).

Major long-term studies in patients with Type 1 diabetes mellitus, at dosages of 2-3 g of nicotinamide per day, have been undertaken recently (ENDIT - see Pociot *et al.*, 1993; IMDIAB III - see Pozzilli *et al.*, 1995; DENIS - see Lampeter *et al.*, 1998). The ENDIT (European Nicotinamide Diabetes Intervention Trial) has reviewed the safety data on nicotinamide before starting the clinical phase, but no results of the trial have yet been published (Pociot *et al.*, 1993; Knip *et al.*, 2000). The IMDIAB III study involved a double-blind trial in which 28 newly diagnosed patients with Type 1 diabetes mellitus were given 25 mg/kg bw of nicotinamide daily for 12 months, and a similar number treated with placebo; no adverse effects were reported and biochemical parameters including liver and kidney function were normal during follow-up (the publication describes the measurement of bilirubin). The DENIS trial (Deutsche Nicotinamide Intervention Study) was a study in young children (average age 3 years) at high risk of developing Type 1 diabetes mellitus in which 25 subjects were randomised to receive nicotinamide (1.2 g per m^2 per day), and 30 to receive placebo; the trial continued for 3 years and during this period all biochemical markers (including alanine aminotransferase, aspartate aminotransferase and bilirubin) were in the normal range.

4.2.4 Glucose intolerance

Nicotinamide has been studied in relation to reducing the risk of the development of diabetes mellitus; none of the studies (see above) has reported a worsening of symptoms in the treated groups.

4.2.5 Other effects and overall dose-response relationships

There have been no other adverse effects reported following the administration of nicotinamide in trials in patients with diabetes. Determination of the NOAEL from the intervention trials is difficult, because of the different dosage regimens employed. Studies have used fixed doses of 1 g/day (Mendola *et al.*, 1989), 1.5 g/day (Chase *et al.*, 1990), 3 g/day (Vague *et al.*, 1987), 25 mg/kg bw/day (IMDIAB III trial) and 1.2 g/m^2/day (DENIS trial). These different doses can be calculated on a body weight basis using the data on body weights or ages in the different publications; the doses approximate to 17 mg/kg bw/day

(Mendola *et al.*, 1989; average age 18.3 years), 37 mg/kg bw/day (Chase *et al.*, 1990; average age 12.5 years), 43 mg/kg bw/day (Vague *et al.*, 1987; adults), 25 mg/kg bw/day (IMDIAB III trial; ages in the range 5-35 years) and 50-40 mg/kg bw/day (DENIS trial; ages 3-12 years). The lowest of these values (25 mg/kg bw/day) was from one of the largest published studies, and this has been used as the NOAEL for nicotinamide.

5. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL

Because of the difference in adverse effect profiles, different upper levels should be developed for nicotinic acid and nicotinamide.

5.1 Nicotinic acid

The more severe forms of toxicity of nicotinic acid, as described above, occur principally at doses of greater than 500 mg/day. The limiting adverse effect at lower doses is flushing, and this has been reported at much lower intakes than the other adverse effects. The most severe and potentially life-threatening adverse effects, such as hepatotoxicity, occur at doses one order of magnitude higher than have been reported for flushing. The dose of free nicotinic acid reported to produce flushing consistently in clinical studies is 50 mg/day (Sebrell and Butler, 1938; Spies *et al.*, 1938). Spies *et al.* (1938) reported a 5% incidence of flushing after a single oral dose of 50 mg nicotinic acid and a 50% incidence at 100 mg. The available data indicate that flushing would be unlikely to occur repeatedly in subjects given less than 50 mg/day, but occasional flushing was reported by Sebrell and Butler (1938) at a dose of 30 mg of nicotinic acid daily. A tolerable upper intake level for nicotinic acid of 10 mg/day is based on the available data indicating occasional flushing at 30 mg per day, using an uncertainty factor of 3 to allow for the fact that a slight effect was reported, and that the study was performed in a small number of subjects, but taking into account the steep dose-response relationship. This upper level is 300-fold below the dose frequently used clinically for the treatment of hypercholesterolaemia (3 g/day) and which is associated with a high incidence of serious adverse reactions. The only reports of flushing associated with the ingestion of nicotinic acid with food have occurred following the addition of free nicotinic acid to food prior to consumption. Although flushing might be considered a minor health effect, it has been used as the basis for setting the upper level for nicotinic acid, because of concerns about the possibility of a transient hypotensive episode, especially in the elderly.

The upper level of 10 mg/day for free nicotinic acid is not applicable during pregnancy or lactation because of inadequate data relating to this critical life stage. The upper levels for intake by children and adolescents have been derived on the basis of their body weights:

Age (years)	Tolerable Upper Intake Level (UL) for nicotinic acid (mg per day)
1-3	2
4-6	3
7-10	4
11-14	6
15-17	8

5.2. Nicotinamide

Nicotinamide does not produce the flushing response that has been used as the basis for the upper level for nicotinic acid. There has been only one reported case of hepatotoxicity in a patient receiving high-dose nicotinamide (however, nicotinamide has not been subject to extensive clinical trials [at 3 g per day or more] for use as a hypolipidaemic agent).

No significant adverse effects have been reported in trials on the possible benefits of nicotinamide in patients with or at risk of diabetes, which have used doses up to the equivalent of 3 g per day, for periods up to 3 years. The NOAEL from these studies is approximately 25 mg/kg bw/day. This value represents the lowest reported dose in a number of recent trials of high quality, many of which used sensitive markers of hepatic function and glucose homeostasis, and included a range of age groups, with some subjects treated with up to 50 mg/kg bw/day. An uncertainty factor of 2 has been used to allow for the fact that adults may eliminate nicotinamide more slowly than the study groups, many of which were children, and that data for children would not reflect the full extent of intersubject variability that could occur in an older population. The upper level for nicotinamide is established at 12.5 mg/kg bw/day or approximately 900 mg/day for adults.

The upper level of 900 mg/day for nicotinamide is not applicable during pregnancy or lactation because of inadequate data relating to this critical life stage. The upper levels for intake by children and adolescents have been derived on the basis of their body weights:

Age (years)	Tolerable Upper Intake Level (UL) for nicotinamide (mg per day)
1-3	150
4-6	220
7-10	350
11-14	500
15-17	700

6. RISK CHARACTERISATION

The form of niacin generally used in vitamin supplements and for addition to foods is nicotinamide. This form does not produce flushing and seems to be of low toxicity compared with nicotinic acid.

The upper level for free nicotinic acid has been derived from data on flushing following administration of a single oral dose given in solution added to tomato juice and consumed with a meal. Flushing has not been reported for the bound forms of nicotinic acid that are present in foods.

The upper levels do not apply to the use of nicotinic acid or nicotinamide under clinical supervision for the treatment of hypercholesterolaemia and hyperlipidaemias or reducing the risk of the development of diabetes.

There are inadequate data on the safety of nicotinic acid or nicotinamide during pregnancy or lactation, and therefore the upper level for adults does not apply to these life stages. However, it is noted that the adverse effect produced by low doses of free nicotinic acid is of a mild and

transient nature and there are no reports of increased susceptibility to this effect during pregnancy or lactation. With regard to nicotinamide, there is no indication that intakes within the range currently consumed in foods, including fortified foods, in European countries are associated with any risk during pregnancy or lactation and there is evidence, at least from one study, that an additional 15 mg is without adverse effect on pregnancy outcome.

7. RECOMMENDATIONS

There is a need for reproductive toxicity studies on both nicotinic acid and nicotinamide.

The upper level for nicotinic acid has been based on the possibility that the flushing detected at higher doses in young subjects could result in transient hypotensive episodes in the elderly. This possibility should be investigated.

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