

## Risk Assessment

## Niacin (Nicotinic Acid and Nicotinamide)

### General information

#### Chemistry

Niacin (vitamin B<sub>3</sub>) is the generic term for nicotinic acid (pyridine 3-carboxylic acid) and nicotinamide (nicotinic acid amide), and the coenzyme forms of the vitamin. Nicotinamide is the active form, 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.

#### Natural occurrence

Free nicotinic acid and nicotinamide are present in nature in only small amounts. Nicotinic acid is mainly bound to macromolecules in plants, while nicotinamide is usually a component of NADP in the animal world. Nicotinic acid can be formed in humans from the metabolism of dietary tryptophan, and so niacin is not really a vitamin providing adequate tryptophan is available.

#### Occurrence in food, food supplements and medicines

Important sources of preformed niacin include beef, pork, wheat flour, maize (corn) flour, eggs and cows' milk. Human milk contains a higher concentration of niacin than cows' milk. In unprepared 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.

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.

In the UK, niacin supplements are generally in the form of nicotinamide. Levels range from 0.25 to 150 mg per daily dose in multi-nutrient supplements and up to 250 mg per daily dose in single nutrient products. Nicotinamide products with a maximum daily dose of 500 mg are only available from pharmacists, and those preparations used to treat specific metabolic disorders are only available on prescription. Nicotinic acid is present in some General Sales List multivitamin preparations at levels up to 100 mg, and is available from the pharmacist to treat muscle cramp, and on prescription for use in hyperlipidaemias.

#### Other sources of exposure

No other sources of exposure have been identified.

## Recommended amounts

The UK RNI for niacin is 6.6 mg niacin equivalent/1000 kcal, equivalent to 17 and 13 mg/day in adult males and females respectively (COMA, 1991). An increment of 2.3 mg/day niacin was recommended for lactating women. Under normal conditions, for an adult, the amount of tryptophan present in dietary protein provides adequate niacin without the need for any preformed vitamin.

## Analysis of tissue levels and niacin status

There is no established laboratory method for the assessment of niacin status. In experimental animals, measurement of whole blood NADP can provide a sensitive indication of niacin depletion, while the determination of the urinary excretion of *N*-methyl nicotinamide and its metabolite methyl pyridone carboxamide offers the only other method available.

## Brief overview of non-nutritional beneficial effects

High dose treatment with nicotinic acid has been shown to reduce plasma cholesterol levels (by an average of 20 to 35%). In the Coronary Drug Project, nicotinic acid was observed to reduce mortality due to a reduction in lethal coronary events. Supplementation studies have been shown to increase NAD<sup>+</sup> concentrations in lymphocytes. DNA strand breaks in lymphocytes exposed to oxygen radicals were shown to decrease proportionately to NAD<sup>+</sup> concentrations.

High dose nicotinamide treatment has also been claimed to offer protection against the development of insulin-dependent diabetes mellitus.

## Function

Niacin is the functional factor of two important coenzymes, NAD and NADP, which activate over 200 dehydrogenases essential to electron transport and other cellular respiratory reactions. Despite their structural similarity, NAD and NADP have quite different metabolic roles. NAD functions as an electron carrier for intracellular respiration as well as a co-factor for enzymes involved in the oxidation of fats and carbohydrates, such as glyceraldehyde 3-phosphate, lactate, pyruvate and  $\alpha$ -ketoglutarate dehydrogenases. NADP functions as a hydrogen donor in reductive biosynthesis, such as in fatty acid and steroid synthesis and like NAD as a cofactor for enzymes, such as in the oxidation of glucose-6-phosphate to ribose 5-phosphate in the pentose phosphate pathway.

## Deficiency

The most common symptoms of niacin deficiency are changes in the skin, mucosa of the mouth, stomach and intestinal tract and the nervous system. The changes in the skin are among the most characteristic in human beings. They are called 'pellagra', which means 'raw skin' and are most pronounced in the parts of skin exposed to sunlight. Other signs and symptoms include dizziness, vomiting, constipation or diarrhoea, and inflammation of the tongue and gastric mucosa. The neurological symptoms can include fatigue, sleeplessness, depression, memory loss and visual impairment.

### Interactions

Interactions of niacin with drugs have been identified. Prolonged treatment of tuberculosis with isoniazid may lead to niacin deficiency due to its competition with pyridoxal phosphate, a co-enzyme necessary for the conversion of tryptophan to niacin.

Nicotinic acid-induced vasodilation, presenting as skin flushing, is inhibited by clonidine, and may exacerbate the vasodilatory effect of ganglion blocking agents. However, ganglion blocking anti-hypertensives are used extremely rarely now.

### Absorption and bioavailability

In humans, niacin is rapidly absorbed from the stomach and intestine by a sodium carrier-mediated mechanism at low concentrations.

### Distribution and metabolism

Niacin circulates in the plasma in the unbound form as both the acid and the amide. Each enters peripheral tissues by passive diffusion, followed by metabolic trapping by conversion to the pyridine dinucleotides, NAD(H) and NADP(H). Most is found as NAD(H) and the oxidised form NAD.

The plasma half-life of nicotinic acid is relatively short, approximately one hour. Animal studies have shown that nicotinic acid rapidly disappears from the blood and is mainly concentrated in the liver, but also in adipose tissue and in the kidneys.

The main metabolites in humans are *N*-methylnicotinamide, *N*-methyl-2-pyridone-5-carboxamide and *N*-methyl-4-pyridone-5-carboxamide.

### Excretion

The pattern of niacin products excreted after ingestion of the vitamin depends largely on the amount and form of niacin ingested and on the niacin status of the individual. However, the two major excretion products in humans are *N*-methylnicotinamide and *N*-methyl-2-pyridone-5-carboxamide, with minor amounts of the unchanged vitamin, nicotinamide-*N*-oxide and 6-hydroxynicotinamide also being excreted.

## Toxicity

### Human data

Reports of nicotinic acid toxicity in humans stem, in the main, from its use in the treatment of hypercholesterolaemia. Most adverse effects are dose related and generally subside with a reduction in dose or the cessation of treatment. Symptoms of acute toxicity include flushing, itching of the skin, nausea, vomiting and gastrointestinal disturbances. Additionally, jaundice, hyperglycemia, abdominal pain, elevated serum bilirubin, alkaline phosphatase and aminotransferase levels can be seen with ingestion of high levels of nicotinic acid (generally intakes of 3,000 mg/day or more) for long periods of

time. In a small number of cases, anorexia, ophthalmological effects, skin hyperpigmentation and precipitation of incipient psychosis have been reported as side effects of nicotinic acid therapy. Sustained release preparations are reported to be more hepatotoxic than the crystalline form.

Evidence is sparse, but there have been case reports of liver dysfunction following long-term high dose (3000–9000 mg) nicotinamide therapy.

#### *Supplementation trials*

Hoffer (1969) reported a range of adverse effects, including headaches, heartburn, nausea, gastrointestinal disturbances and fatigue at doses of 3000 mg supplemental nicotinamide/day for 3–36 months. However, few details were provided and comparison with controls was lacking. Other supplementation trials (Vague *et al.*, 1987; Mendola *et al.*, 1989; Chase *et al.*, 1990; Pozzilli *et al.*, 1995; Lampeter *et al.*, 1998) have reported no adverse effects at intakes of nicotinamide up to 3000 mg/day. However the studies in which the highest doses were given were primarily of beneficial effect in Type 1 diabetes mellitus patients and it is unclear how information on adverse effects was ascertained. Gastrointestinal effects and flushing have been reported at intakes of 50 mg supplemental nicotinic acid/day and above.

Doses of up to 2000 mg/day of nicotinic acid have reportedly been administered during pregnancy to niacin deficient women in developing countries, without evidence of foetal toxicity (Moghissi, 1981).

#### **Animal data**

Few data are available concerning the ingestion of nicotinic acid. Acute effects in dogs, associated with intake of 2000 mg/day for less than 20 days, included weight loss, blood in the faeces and convulsions resulting in death with associated gastrointestinal and central nervous system changes. With administration of lower doses (up to 1000 mg/day) for 8 weeks dogs gained weight and appeared in good health. Traces of albumin and sugar were found in urine.

Chronic administration of 1% nicotinamide in the diet to rats has been shown to inhibit growth.

#### **Reproductive toxicity**

In rats, ingestion of nicotinamide has been shown to cause growth retardation, which may be due, in part, to the reduced intake of food and water due to the palatability and in part to a deficiency in methionine, which is expended during the methylation of nicotinamide into its metabolites.

#### **Carcinogenicity and genotoxicity**

No carcinogenicity data are available for nicotinic acid.

In lifetime studies in the mouse, nicotinamide alone was not carcinogenic. However, in combination with streptozotocin, nicotinamide has been shown to cause islet cell tumours in rats. The resulting oncogenicity is likely to be the result of an imbalance between the degree of DNA damage and the level of inhibition of DNA repair.

No genotoxicity data are available for nicotinic acid or nicotinamide.

### Dose response characterisation

Few data are available, but supplemental intakes of nicotinamide of up to 3000 mg/day appear to be well tolerated. Flushing has been reported with bolus doses of nicotinic acid of 10 mg or higher, but flushing is more consistently associated with supplemental intakes of nicotinic acid of 50 mg/day and above.

### Mechanisms of toxicity

No relevant data have been identified.

### Vulnerable groups

Individuals with hepatic dysfunction or a history of liver disease, diabetes mellitus, active peptic ulcer disease, gout, cardiac arrhythmias, migraine headaches and alcoholism may be particularly susceptible to nicotinic acid effects.

### Genetic variations

No data on genetic variations that increase vulnerability to niacin toxicity have been identified.

## Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

### Human data – nicotinic acid

#### *Spies et al., 1938*

In an uncontrolled study, 100 adult subjects were given single oral doses of 50 or 100 mg nicotinic acid on an empty stomach. Flushing, burning and itching was reported in 5% of those receiving the 50 mg dose and 50 % of those given 100 mg. Flushing occurred in the majority of subjects receiving 200 mg doses of nicotinic acid and was present 'to some extent' in all subjects receiving 500 mg doses. It is unclear how the subjects were divided between dose groups. By studying cutaneous temperatures, it was determined that the increase was most marked over the ears and neck and less pronounced over the trunk, with the extremities being least affected.

#### *Sebrell and Butler, 1938*

In an uncontrolled study, groups of six subjects were given 10, 30 or 50 mg nicotinic acid daily for three months. Flushing was reported intermittently in 0, 2 and 4 individuals, respectively. The subjects received an identical diet. The authors noted that there was considerable inter-individual variation, which was not accounted for by body weight.

*The Coronary Drug Project, 1975*

The study was conducted to investigate the possible use of nicotinic acid in coronary heart disease to reduce the incidence of a second myocardial infarction. The study demonstrated little immediate beneficial effect, but considerable toxicity. One third to one half of the 1119 patients taking 3000 mg nicotinic acid/day for at least five years had increased serum levels of liver enzymes. An elevation in serum uric acid levels was noted in the nicotinic acid treated group (44% of nicotinic acid treated individuals) and an increased incidence of acute gouty arthritis (6.4% of nicotinic acid treated individuals), compared to controls (4.3% of individuals). Consistent with other reports, side effects included dermatological problems of flushing, itching and rash. Other significant complaints in nicotinic acid-treated individuals included gastrointestinal and urinary tract problems.

*Knopp et al., 1985*

A study in 71 patients compared the effects of regular nicotinic acid (37 individuals) and sustained release nicotinic acid (34 individuals). Treatment was for six months and subjects received an initial dose of 1500 mg/day, increasing to 3000 mg/day from the second month. However, due to a higher frequency of side effects among those receiving the sustained release formula, the daily intake was reduced to 2000 mg/day for this group. Subjects treated with sustained release nicotinic acid experienced a significantly higher rate of gastrointestinal effects, compared with those on regular nicotinic acid. Dermatological problems were reported for both treatments.

*Fraunfelder et al., 1995*

In a retrospective survey, 102 patients taking nicotinic acid medication (3000-8000 mg/day) for hyperlipidaemia were more likely than those taking other lipid lowering agents to report blurred vision (26%), dry eyes (20%), eyelid oedema (10%) and macular oedema (2%). The ocular side effects were all reversible if treatment was discontinued and the authors reported the severity of effects to be dose dependent. For one patient, a reduction in dose from 3000 mg/day to 1500 mg/day was stated to have reversed the effects on her vision.

**Human data – nicotinamide***Vague et al., 1987*

In a study published as a letter, no adverse effects were reported in a double-blind trial in 16 Type 1 diabetics who received 3000 mg nicotinamide per day or placebo for six months. The average age of the subjects was 22.1 years in the treatment group and 24.8 years in the placebo group. No adverse effects were noted but it is unclear how this was ascertained.

*Mendola et al., 1989*

In a single-blind trial, twenty newly diagnosed Type 1 diabetics, received 1000 mg nicotinamide/day or placebo for 45 days. The average age of the subjects was 18.3 years in the treatment group and 15.5 years in the placebo group. No adverse effects were observed when physiological, biochemical and haematological parameters were assessed.

*Chase et al., 1990*

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 1500 mg/day for 12 months. The authors stated that no significant adverse effects were encountered with the use of nicotinamide, although it is unclear how information on side effects was ascertained.

*Pozzilli et al., 1995*

In a double-blind trial following up the work of Mendola, a further 56 newly diagnosed Type I diabetics aged 5-35 years were given 25 mg/kg bw/day or placebo for 12 months. It was stated that biochemical tests including liver and kidney function were normal during follow up and that no adverse effects were noted in either treated or placebo patients.

*Lampeter et al., 1998*

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 supplemental nicotinamide (1200 mg/m<sup>2</sup>/day) for a maximum duration of 3.8 years. Mean treatment time was 2.1 years. If it is assumed that the children in the study were of average height and weight, a total nicotinamide intake, including the contribution of the diet, of 1260 mg/day or 42 mg/kg bw/day can be estimated in subjects receiving the nicotinamide supplement. The rates of diabetes onset were the same throughout the observation period in both groups. All biochemical and haematological parameters (alanine aminotransferase, aspartate aminotransferase, bilirubin, blood sedimentation rate,  $\gamma$ -glutamyl transferase, urea, uric acid, creatinine and lactate dehydrogenase) were within the normal range, and means did not differ between the groups throughout the study.

## Exposure assessment

The exposure data below for intake from food are for niacin equivalents. These are defined as the niacin content of the food plus 1/60th the content of tryptophan, as nicotinic acid is formed in the body from the metabolism of tryptophan. It is not possible to distinguish the two forms of niacin in this survey data.

Food	Mean: 34 mg/day (from 1986/87 NDNS) 97.5th percentile: 57 mg/day
Supplements	up to 250 mg/day (as nicotinamide, or up to 150 mg/day as nicotinic acid) (Annex 4; OTC, 2001)
Estimated maximum intake of niacin equivalents:	57 + 250 = 307 mg/day.

No potential high intake groups have been identified.

## Risk assessment

### Nicotinic acid

Large doses of nicotinic acid are associated with a number of adverse effects in man. These have been identified from the use of nicotinic acid in the treatment of hypercholesterolaemia. The effects reported include flushing, skin itching, nausea, vomiting and gastrointestinal disturbance. The effects are dose related and reversible on cessation of treatment.

At higher intakes of nicotinic acid over long periods of time, liver dysfunction has been reported. Symptoms such as elevated liver enzymes, elevated bilirubin levels and jaundice have been observed. Other adverse effects reported include hyperglycaemia and adverse ophthalmological effects such as blurred vision and cystoid macular oedema. No relevant animal data have been reported and the mechanism for nicotinic acid-induced toxicity is unclear.

### Nicotinamide

Fewer data are available on the safety of nicotinamide. Studies in Type I diabetics have suggested that doses of up to 3000 mg/day nicotinamide are not associated with adverse effects, although these investigations involved small numbers of subjects and it is unclear from the studies in which the highest doses were given how adverse effects would have been ascertained. Since the studies were undertaken in diabetics or in individuals at high risk of developing diabetes the applicability of the results to the general population is unclear. No relevant animal data have been identified.

### ESTABLISHMENT OF GUIDANCE LEVEL – NICOTINIC ACID

There are insufficient data from human or animal studies to establish a Safe Upper Level for nicotinic acid.

Numerous reports exist, including both case reports and controlled clinical trials, in which doses of approximately 3000 mg/day nicotinic acid have apparently caused hepatotoxic effects. For example, in a randomised double-blind study, one third or more of 1119 patients who received 3000 mg nicotinic acid/day for up to 5 years were reported to have elevated levels of liver enzymes. Elevations in serum uric acid levels and an increased incidence of gout were also reported.

Flushing has been consistently reported at intakes of 50 mg/day and above (Spies *et al.*, 1938; Sebrell and Butler, 1938). If 50 mg/day is taken as a LOAEL and an uncertainty factor of 3 is applied to extrapolate to a NOAEL, then a guidance level, for supplementation only, of  $50/3 = 17$  mg/day (equivalent to 0.28 mg/kg bw/day in a 60 kg adult) for nicotinic acid is derived. This guidance level is given for supplements only, as adverse effects appear to be related to acute, bolus intakes of nicotinic acid, rather than more sustained exposure as would occur with ingestion of nicotinic acid via food. Free nicotinic acid levels in food are low.

It should be noted that this guidance level is based on intakes of conventional formulations of nicotinic acid and, therefore, would not be applicable to sustained release preparations. Nicotinic acid contained in dietary supplements is not in the sustained release form, which is thought to be more hepatotoxic.

### ESTABLISHMENT OF GUIDANCE LEVEL- NICOTINAMIDE

There are insufficient data from human or animal studies to establish a safe upper level for nicotinamide.

From the limited existing database the occurrence of nicotinamide toxicity appears to be quite low. Large doses of nicotinamide (up to 3000 mg/day for periods of up to 3 years) appear to be well tolerated, as reported in numerous trials on the possible benefits of nicotinamide in patients with, or at risk of developing, diabetes. These trials, however, usually studied only one dose level, and the numbers of subjects involved in the trials was small. Two of the best conducted studies are those by Pozzilli *et al.* (1995) and Lampeter *et al.* (1998) and we have used these for guidance purposes. In these studies, doses of 25 and 42 mg/kg bw/day did not affect a range of biochemical parameters, including liver and kidney function tests in small groups of Type 1 diabetics (or those at high risk of developing the condition). Although no adverse effects were detected, the nature of the study population and the small numbers involved mean that these findings may not be applicable to the whole population. Although no adverse effects were identified, it is prudent in this case to apply a UF of 3 to account for inter-individual variability because of the nature of the study population. Thus,  $25/3$  results in a guidance value, for supplementation only, of 8.3 mg/kg bw/day for nicotinamide. This is equivalent to 500 mg/day supplemental nicotinamide in a 60 kg adult.

Assuming a maximum intake of 57 mg/day from food, a total dose of 560 mg/day (equivalent to 9.3 mg/kg bw/day in a 60 kg adult) would not be expected to result in any adverse effects. There is a lack of data on the safety of nicotinamide in pregnancy, and no relevant animal data. This level does not therefore apply to pregnant women.

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