



## Introduction

The term niacin refers to both nicotinic acid and its amide derivative, nicotinamide (niacinamide). Both are used to form the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Niacin is a member of the water soluble B-vitamin complex. The amino acid tryptophan can be converted to nicotinic acid in humans, therefore niacin is not really a vitamin provided that an adequate dietary supply of tryptophan is available.

Nicotinic acid was isolated as early as 1867. In 1937 it was demonstrated that this substance cures the disease pellagra. The name niacin is derived from nicotinic acid + vitamin.

## Functions

The coenzymes NAD and NADP are required for many biological oxidation-reduction (redox) reactions. About 200 enzymes require NAD or NADP. NAD is mainly involved in reactions that generate energy in tissues by the biochemical degradation of carbohydrates, fats and proteins. NADP functions in reductive biosyntheses such as the synthesis of fatty acids and cholesterol.

NAD is also required as a substrate for non-redox reactions. It is the source of adenosine diphosphate (ADP)-ribose, which is transferred to proteins by different enzymes. These enzymes and their products seem to be involved in DNA replication, DNA repair, cell differentiation and cellular signal transduction.

### Main functions in a nutshell:

- Coenzymes (NAD and NADP) in redox reactions
- NAD is a substrate for non-redox reactions

## Dietary sources

Nicotinamide and nicotinic acid occur widely in nature. Nicotinic acid is more prevalent in plants, whereas in animals nicotinamide predominates. Yeast, liver, poultry, lean meats, nuts and legumes contribute most of the niacin obtained from food. Milk and green leafy vegetables contribute lesser amounts.

In cereal products (corn, wheat), nicotinic acid is bound to certain components of the cereal and is thus not bioavailable. Specific food processing, such as the treatment of corn with lime water involved in the traditional preparation of tortillas in Mexico and Central America, increases the bioavailability of nicotinic acid in these products.

Tryptophan contributes as much as two thirds of the niacin activity required by adults in typical diets. Important food sources of tryptophan are meat, milk and eggs.

### Niacin content of foods

Food	Niacin (mg/100g)
Veal liver	15
Chicken	11
Beef	7.5
Salmon	7.5
Almonds	4.2
Peas	2.4
Potatoes	1.2
Peach	0.9
Tomatoes	0.5
Milk (whole)	0.1

(Souci, Fachmann, Kraut)

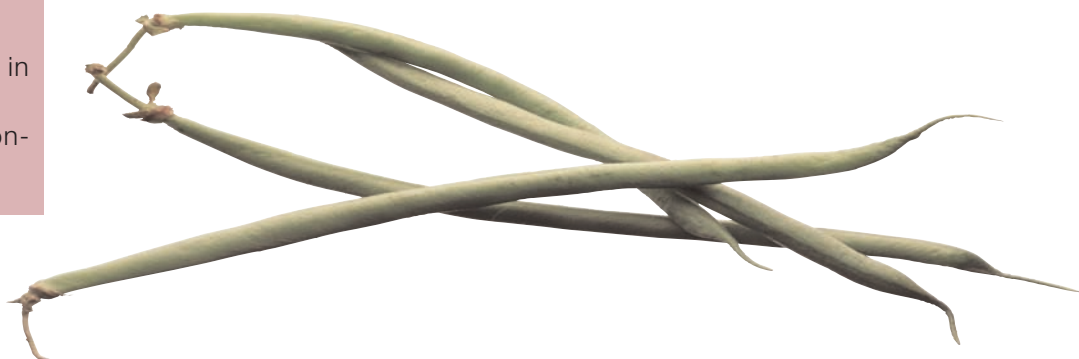
## Absorption and body stores

Both acid and amide forms of the vitamin are readily absorbed from the stomach and the small intestine. At low concentrations the two forms are absorbed by a sodium-dependent facilitated diffusion, and at higher concentrations by passive diffusion. Niacin is present in the diet mainly as NAD and NADP, and nicotinamide is released from the coenzyme forms by enzymes in the intestine. The main storage organ, the liver, may contain a significant amount of the vitamin, which is stored as NAD. The niacin coenzymes NAD and NADP are synthesised in all tissues from nicotinic acid or nicotinamide.

## Measurement

Determination of the urinary excretion of two niacin metabolites, N-methyl-nicotinamide and N-methyl-2-pyridone-5-carboxamide has been used to assess niacin status. Excretion of  $5.8 \pm 3.6$  mg N-methyl-nicotinamide/24hrs and  $20.0 \pm 12.9$  mg N-methyl-2-pyridone-5-carboxamide/24hrs are considered normal.

Recent studies suggest that the measurement of NAD and NADP concentrations and their ratio in red blood cells may be sensitive and reliable indicators for the determination of niacin status. A ratio of erythrocyte NAD to NADP  $< 1.0$  may identify subjects at risk of developing niacin deficiency.



## Stability

Both nicotinamide and nicotinic acid are stable when exposed to heat, light, air and alkali. Little loss occurs in the cooking and storage of foods.

## Interactions

### Negative interactions

Copper deficiency can inhibit the conversion of tryptophan to niacin. The drug penicillamine has been demonstrated to inhibit the tryptophan-to-niacin pathway in humans; this may be due in part to the copper-chelating effect of penicillamine. The pathway from tryptophan to niacin is sensitive to a variety of nutritional alterations. Inadequate iron, riboflavin, or vitamin B<sub>6</sub> status reduces the synthesis of niacin from tryptophan.

Long-term treatment of tuberculosis with isoniazid may cause niacin deficiency because isoniazid is a niacin antagonist. Other drugs which interact with niacin metabolism may also lead to niacin deficiency, e.g. tranquilisers (diazepam) and anticonvulsants (phenytoin, phenobarbital).

## Deficiency

Symptoms of a marginal niacin deficiency include: insomnia, loss of appetite, weight and strength loss, soreness of the tongue and mouth, indigestion, abdominal pain, burning sensations in various parts of the body, vertigo, headaches, numbness, nervousness, poor concentration, apprehension, confusion and forgetfulness.

Severe niacin deficiency leads to pellagra, a disease characterised by dermatitis, diarrhoea and dementia. In the skin, a pigmented rash develops symmetrically in areas exposed

to sunlight (the term pellagra comes from the Italian phrase for raw skin). Symptoms affecting the digestive system include a bright red tongue, stomatitis, vomiting, and diarrhoea. Headaches, fatigue, depression, apathy, and loss of memory are neurological symptoms of pellagra. If untreated, pellagra is fatal.

Since the synthesis of NAD from tryptophan requires an adequate supply of riboflavin and vitamin B<sub>6</sub>, insufficiencies of these vitamins may also contribute to niacin deficiency, resulting in pellagra.

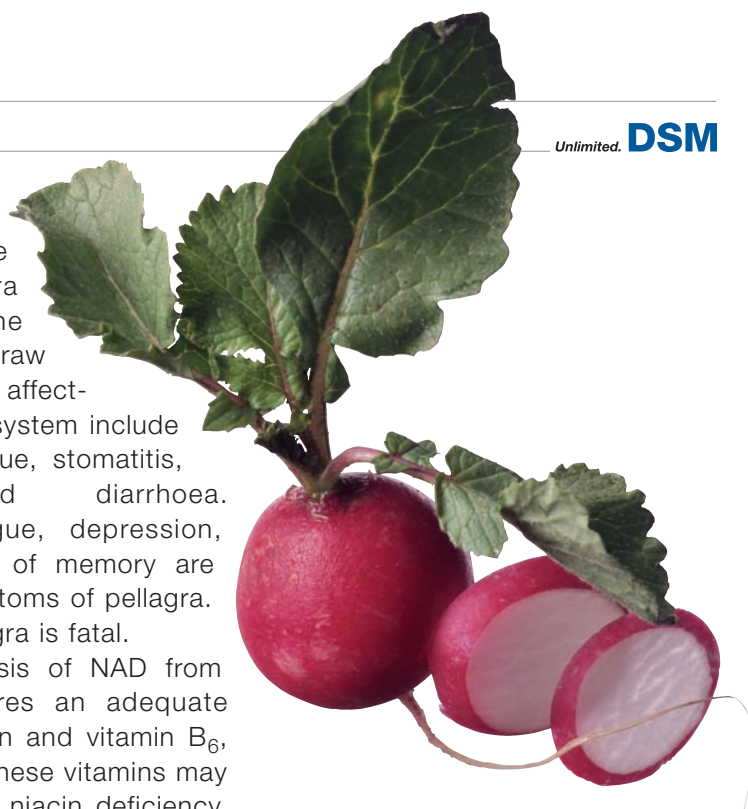
Pellagra is rarely seen in industrialised countries, except for its occurrence in people with chronic alcoholism. In other parts of the world where maize and jowar (barley) are the major staples, pellagra persists. It also occurs in India and parts of China and Africa.

Patients with Hartnup's disease, a genetic disorder, develop pellagra because their absorption of tryptophan is defective. Carcinoid syndrome may also result in pellagra because dietary tryptophan is preferentially used for serotonin synthesis and NAD synthesis is therefore restricted.

## Disease prevention and therapeutic use

Niacin is specific in the treatment of glossitis, dermatitis and the mental symptoms seen in pellagra.

High doses of nicotinic acid (1.5-4 g/day) can reduce total and low-density lipoprotein cholesterol and triacylglycerols and increase high-density lipoprotein cholesterol in patients at risk of cardiovascular disease. There is a flush reaction to high doses of nicotinic acid, which is



seen primarily with a rising blood level and may wear off once a plateau level has been reached.

Nicotinic acid has also been used in doses of 100 mg as a vasodilator in patients suffering from diseases causing vasoconstriction.

Type 1 diabetes mellitus results from the autoimmune destruction of insulin-secreting  $\beta$ -cells in the pancreas. There is evidence that nicotinamide may delay or prevent the development of diabetes. Clinical trials are in progress to investigate this effect of nicotinamide.

Recent studies suggest that infection with human immunodeficiency virus (HIV) increases the risk of niacin deficiency. Higher intakes of niacin were associated with decreased progression rate to AIDS in an observational study of HIV-positive men.

DNA damage is an important risk factor for cancer. NAD is consumed as a substrate in ADP-ribose transfer reactions to proteins which play a role in DNA repair. This has aroused interest in the relationship between niacin and cancer. A large case-control study found increased consumption of niacin, along with antioxidant nutrients, to be associated with decreased incidence of cancers of the mouth, throat and oesophagus.

## Recommended Dietary Allowance (RDA)

The actual daily requirement of niacin depends on the quantity of tryptophan in the diet and the efficiency of the tryptophan to niacin conversion. The conversion factor is 60 mg of tryptophan to 1 mg of niacin, which is referred to as 1 niacin equivalent (NE). This conversion factor is used for calculating both dietary contributions from tryptophan and recommended allowances of niacin.

In the USA, the RDA for adults is 16 mg NEs for men and 14 mg NEs for women. Other regulatory authorities have established similar RDAs.

## Safety

There is no evidence that niacin from foods causes adverse effects. Pharmacological doses of nicotinic acid, but not nicotinamide, exceeding 300 mg per day have been associated with a variety of side effects

including nausea, diarrhoea and transient flushing of the skin. Doses exceeding 2.5 g per day have been associated with hepatotoxicity, glucose intolerance, hyperglycaemia, elevated blood uric acid levels, heartburn, nausea, headaches. Severe jaundice may occur, even with doses as low as 750 mg per day, and may eventually lead to irreversible liver damage. Doses of 1.5 to 5 g/day of nicotinic acid have been associated with blurred vision and other eye problems.

Tablets with a buffer and time release capsules are available to reduce flushing and gastrointestinal irritation for persons with a sensitivity to nicotinic acid. These should be used with caution, however, because time-release niacin tablets used at high levels are linked to liver damage.

The Food and Nutrition Board (1998) set the tolerable upper intake level (UL) for niacin (nicotinic acid plus nicotinamide) at 35 mg/day. The EU Scientific Committee on Food (2002) developed different upper levels for nicotinic acid and nicotinamide: the UL for nicotinic acid has been set at 10 mg/day, for nicotinamide at 900 mg/day.

## Supplements and food fortification

Single supplements of nicotinic acid are available in tablets, capsules and syrups. Multivitamin and B-complex vitamin infusions, tablets and capsules also contain nicotinamide.

Niacin is used to fortify grain including corn and bran breakfast cereals and wheat flour (whole meal, white and brown). US standards of identity and state standards require enrichment of bread, flour, farina, macaroni, spaghetti and noodle products, corn meal, corn grits and rice.

## Industrial production

Although other routes are known, most nicotinic acid is produced by oxidation of 5-ethyl-2-methylpyridine. Nicotinamide is produced via 3-methylpyridine. This compound is derived from two carbon sources, acetaldehyde and formaldehyde, or from acrolein plus ammonia. 3-Methylpyridine is first oxidised to 3-cyanopyridine, which in a second stage converts to nicotinamide by hydrolysis.

### Current recommendations in the USA

#### RDA\*

Infants	< 6 months	2mg (AI)
Infants	7-12 months	4mg (AI)
Children	1-3 years	6mg
Children	4-8 years	8mg
Children	9-13 years	12mg
Males	> 14 years	16mg
Females	> 14 years	14mg
Pregnancy		18mg
Lactation		17mg

\*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

## History

- 1755** The disease pellagra is first described by Thiery who calls the disease “mal de la rosa”.
- 1867** Huber provides the first description of nicotinic acid.
- 1873** Weidel describes the elemental analysis and crystalline structure of the salts and other derivatives of nicotinic acid in some detail.
- 1894** First preparation of nicotinamide by Engler.
- 1913** Funk isolates nicotinic acid from yeast.
- 1915** Goldberger demonstrates that pellagra is a dietary deficiency disease.
- 1928** Goldberger and Wheeler use the experimental model of black tongue disease in dogs as an experimental model for the human disease pellagra.
- 1937** Elvehjem and coworkers show the effectiveness of nicotinic acid and nicotinamide in curing canine black tongue.
- 1937** Spies cures human pellagra using nicotinamide.
- 1945** Krehl discovers that the essential amino acid tryptophan is transformed into niacin by mammalian tissues.
- 1955** The concept of niacin equivalents is proposed by Horwitt.
- 1955** Altschul and associates report that high doses of nicotinic acid reduce serum cholesterol in man.
- 1961** Turner and Hughes demonstrate that the main absorbed form of niacin is the amide.
- 1979** Shepperd and colleagues report that high doses of nicotinic acid lower both serum cholesterol and triglycerides.
- 1980** Bredehorst and colleagues show that niacin status affects the extent of ADP-ribosylation of proteins.



Casimir Funk



Conrad Elvehjem



Tom Spies