Nickel is available in some multivitamin preparations, typically at a dose of about 5 micrograms. Nickel may also be present in colloidal or liquid mineral supplements.

In NHANES III, the adult median intake of nickel from supplements was approximately 5 micrograms/day.

Except for tolerable upper intake levels (UL—see table below), no DRI (dietary reference intake) has yet been established for nickel.

The Food and Nutrition Board of the U.S. National Academy of Sciences has published the following Dietary Reference Intakes (DRI) for nickel. A summary of DRIs for various age groups is as follows:

DRI values (milligrams/day)

Infants	UL
0-6 months	ND
7-12 months	ND
Children	
1-3 years	0.2
4-8 years	0.3
Boys	
9-13 years	0.6
14-18 years	1.0
Girls	
9-13 years	0.6
14-18 years	1.0
Men	
19-30 years	1.0
31-50 years	1.0
51-70 years	1.0
Older than 70 years	1.0
Women	
19-30 years	1.0
31-50 years	1.0
51-70 years	1.0
Older than 70 years	1.0
Pregnancy	
14-18 years	1.0
19-30 years	1.0
31-50 years	1.0
Lactation	
14-18 years	1.0
19-30 years	1.0
31-50 years	1.0

ND = Not Determinable. The value is not determinable because of the lack of data on adverse effects in this age group and concern regarding the lack of ability to handle excess amounts. To prevent high levels of intake, the only source of nickel for infants should be from food and formula.

There are no Recommended Dietary Allowances (RDA), Estimated Average Requirements (EAR) or Adequate Intake levels established for nickel.

The UL is the Tolerable Upper Intake Level and usually represents the total intake from food, water and supplements.

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Nicotinamide

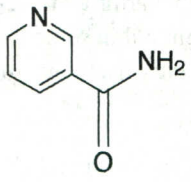
DESCRIPTION

Nicotinamide (niacinamide) is one of the two principal forms of the B-complex vitamin niacin (see Niacin). The term niacin is used as a collective term to refer to both nicotinamide and nicotinic acid, the other principal form of niacin, or the term is used synonymously with nicotinic acid. Nicotinamide and nicotinic acid have identical vitamin activities, but they have very different pharmacological activities.

Nicotinamide, via its major metabolite NAD^+ (nicotinamide adenine dinucleotide), is involved in a wide range of biological processes, including the production of energy, the synthesis of fatty acids, cholesterol and steroids, signal transduction and the maintenance of the integrity of the genome. Nicotinic acid, in pharmacological doses, is used as an antihyperlipidemic agent. It also causes vasodilation of cutaneous blood vessels resulting in the so-called niacin flush. Nicotinamide in pharmacological doses does not have antihyperlipidemic activity, nor does it cause a niacin-flush. There is evidence, however, that pharmacological doses of

nicotinamide may prevent type 1 diabetes mellitus. And, interestingly, pyrazinamide, an important drug in the treatment of tuberculosis, is an analogue of and shares the same biochemical mechanism with nicotinamide.

Nicotinamide, in addition to being known as niacinamide, is also known as 3-pyridinecarboxamide, pyridine-3-carboxamide, nicotinic acid amide, vitamin B_3 and vitamin PP. Its molecular formula is $C_6H_6N_2O$ and its molecular weight is 122.13 daltons and the structural formula is:



Nicotinamide

Nicotinamide is the principal form of niacin used in nutritional supplements and in food fortification. See also Niacin (Nicotinic Acid).

ACTIONS AND PHARMACOLOGY

ACTIONS

Nicotinamide may have anti-diabetogenic activity in some. It may also have antioxidant, anti-inflammatory and anticarcinogenic activities. Nicotinamide has putative activity against osteoarthritis and granuloma annulare.

MECHANISM OF ACTION

Nicotinamide is being investigated as an agent for the possible prevention or delaying of the onset of type 1 diabetes mellitus (insulin-dependent diabetes mellitus or IDDM). The rationale for using nicotinamide to prevent type 1 diabetes mellitus is derived from human and animal studies as well as *in vitro* investigations. Nicotinamide has been found to prevent diabetes in alloxan- and streptozotocin-treated mice and rats and in non-obese diabetic (NOD) mice. *In vitro* studies have shown that nicotinamide can prevent macrophage- or interleukin-1beta-induced beta-cell damage. An intervention study in New Zealand using nicotinamide treatment showed a 50% reduction in the development of IDDM over a five-year period.

The mechanism of the possible anti-diabetogenic activity of nicotinamide is not well understood. The pathogenesis of IDDM involves the autoimmune destruction of beta-cells, which is accompanied by the appearance of beta-cell specific antibodies, such as islet cell antibodies (ICA) and antibodies to glutamic acid decarboxylase (GAD), many years before the onset of the disease. Macrophages and T lymphocytes are the first cells to appear in the islets of the pancreas during the development of autoimmune diabetes. It is thought that cytokines released by macrophages/monocytes, such as interleukin (IL)-12 and tumor necrosis factor (TNF)-alpha, might play a role in early beta-cell damage. IL-12 may play a role in the initiation of the autoimmune process by enhancing T helper 1 lymphocyte (Th1) responses. Nicotinamide has been shown to decrease the production of IL-12 and TNF-alpha in cultures of whole blood from prediabetic and diabetic subjects and also in healthy controls. Inhibition of IL-12 production by nicotinamide could play an important role in the modulation of the immune response leading to IDDM. Further, since the cytokine-inhibitory activity was observed in healthy controls, as well as in prediabetic and diabetic subjects, nicotinamide may have application in other autoimmune disorders.

Nicotinamide has been demonstrated, in one study, to affect glucose tolerance and insulitis in NOD mice, slowing down diabetes progression. In this study, nicotinamide decreased MHC class II expression (but not MHC class I), enhanced intercellular adhesion molecule-1 (ICAM-1) expression, counteracted the fall of superoxide dismutase (observed in untreated NOD mice) and increased the levels of interleukin (IL)-4, a T helper 2 lymphocyte (Th2) protective cytokine.

The anti-diabetogenic effect of nicotinamide may be due, in part, to an increase in the pool size of NAD^+ in beta-cells. NAD^+ is the principal metabolite of nicotinamide. It appears that the pool size of NAD^+ in beta-cells in pre-diabetics and diabetics is significantly reduced. Damage and destruction of beta-cells may occur via oxidative stress. Increased levels of reactive oxygen species in beta-cells may result in, among other things, oxidative damage to DNA resulting in DNA strand breaks. The enzyme poly(ADP-ribose)polymerase or PARP is believed to play a role in DNA repair. PARP uses NAD^+ as its substrate. In the context of a reduced level of NAD^+, PARP activity may essentially use most of the cellular NAD^+. This could result in cellular apoptosis. Nicotinamide is an inhibitor of PARP. It also has antioxidant activity and, of course, is metabolized to NAD^+. All of these effects may play some role in the possible anti-diabetogenic action of nicotinamide.

Nicotinamide has been shown to have antioxidant activity. *In vitro*, it has been found to inhibit protein oxidation and lipid peroxidation. It has also been found to inhibit reactive oxygen species-induced apoptosis, to inhibit phagocytic generation of reactive oxygen species, to scavenge reactive oxygen species and to inhibit the oxidative activity of nitric oxide.

Nicotinamide has demonstrated a number of anti-inflammatory activities. Nicotinamide has been shown to inhibit lipopolysaccharide-induced TNF-alpha in the mouse, in a dose-dependent manner. It is thought that this inhibition of

TNF-alpha is mediated via inhibition, at the gene transcription level, of NF-Kappa B, which in turn inhibits TNF-alpha. Nicotinamide has also been shown to decrease the production of IL-12 and TNF-alpha in cultures of whole blood from prediabetic and diabetic subjects and also in healthy subjects.

Niacin deficiency has been found to inhibit DNA repair in cell culture models. NAD^+ is the substrate for PARP, an enzyme thought to be involved in DNA repair. Extensive damage to DNA may result in depletion of NAD^+ secondary to its use by PARP. Depletion of NAD^+ may trigger cellular apoptosis. DNA repair by PARP, as well as its possible role in apoptosis, may contribute to protection against carcinogenesis. These mechanisms may account, in part, for the possible anticarcinogenic activity of nicotinamide. Nicotinamide, via NAD^+, modulates the expression of the p53 tumor suppressor protein in human breast, lung, skin and lung cells. This is another mechanism for nicotinamide's possible anticarcinogenic activity.

A pilot study suggests that nicotinamide may be beneficial in some with osteoarthritis. The mechanism of this putative activity is unknown. The mechanism of the putative activity of nicotinamide in granuloma annulare is also unknown.

PHARMACOKINETICS

Nicotinamide is efficiently absorbed from the gastrointestinal tract. At low doses, absorption is mediated via sodium-dependent facilitated diffusion. Passive diffusion is the principal mechanism of absorption at higher doses. Doses of up to three to four grams of nicotinamide are almost completely absorbed. Nicotinamide is transported via the portal circulation to the liver and via the systemic circulation to the various tissues of the body. Nicotinamide enters most cells by passive diffusion and enters erythrocytes by facilitated transport.

Nicotinamide is metabolized to NAD^+ which in turn has a number of metabolic opportunities, including the formation of nicotinamide, $NADP^+$ (nicotinamide adenine dinucleotide phosphate), NMN (nicotinamide 5'-mononucleotide), cyclic ADP-ribose and NAADP (nicotinic acid dinucleotide phosphate). NAD^+ also serves as the substrate for mono(ADP-ribosyl)ation and poly(ADP-ribosyl)ation. Poly(ADP-ribosyl)ation is catalyzed by PARP. Nicotinamide may be converted to nicotinic acid via the enzyme nicotinamidase.

In the liver, the principal catabolic products of high-dose nicotinamide are N'-methylnicotinamide, N'-methyl-5-carboxamide-2-pyridone, N'-methyl-5-carboxamide-4-pyridone and nicotinamide-N-oxide. High-dose nicotinamide is excreted in the urine as unchanged nicotinamide, N'-methylnicotinamide, N'-methyl-5-carboxamide-2-pyridone, N'-methyl-5-carboxamide-4-pyridone and nicotinamide-N-oxide.

INDICATIONS AND USAGE

Nicotinamide, unlike nicotinic acid (niacin), does not have significant effects on lipids, and its efficacy in diabetes is unclear. It demonstrates antiinflammatory properties, and it is emerging as a possible potent neuroprotective agent. It may also be an effective depigmenter in some with skin hyperpigmentation. It was recently shown to suppress hyperphosphatemia in hemodialysis patients. There is preliminary evidence it might help some with generalized granuloma annulare and osteoarthritis, but little evidence that it is helpful in rheumatoid arthritis or schizophrenia. There is a suggestion that it might aid in some cancer therapies. There is little evidence that it is useful in tinnitus.

RESEARCH SUMMARY

Nicotinamide was shown to protect the non-obese diabetic (NOD) mouse from type 1 (IDDM) diabetes if given early enough and at high enough doses. It was hoped that nicotinamide might similarly intervene in human type 1 diabetes as evidenced, among other things, by its observed ability to protect isolated islets of Langerhans *in vitro* from various toxic agents. *In vitro* experiments also showed that nicotinamide could reduce beta cell impairment and death caused by macrophages and exposure to various cytokines involved in this autoimmune disease.

Since nicotinamide has not been shown to have significant, prolonged effects when introduced after the onset of type 1 diabetes, its efficacy has been researched as an interventive therapy. It shows some ability to extend the remission phase when administered to subjects newly diagnosed with the disease. During the remission phase, the need for exogenous insulin is decreased or obliterated, but insulin-dependence reasserts itself, usually within one year despite nicotinamide supplementation. On the other hand, nicotinamide appears to be far more effective as a preventive.

In one 5-year intervention study, nicotinamide was administered prior to the clinical onset of IDDM. Using antibody markers that predict the onset of IDDM within 5 years, 150 young subjects were selected to receive nicotinamide at a dose of 1.2 grams per square meter of body surface area daily. It was concluded that nicotinamide supplementation reduced the expected incidence of IDDM 50% over a 5-year period. After all this positive news, it was hoped that nicotinamide might continue to show benefit in a larger, better-controlled study of type 1 (insulin-dependent) diabetes. However, high-dose nicotinamide has now failed to provide protection in a double-blind, placebo-controlled, randomized trial in individuals with a first-degree family history of type-1 diabetes. This five-year study involved 552 individuals. Of 159 participants who developed diabetes during the study period, 82 were taking nicotinamide and 77

were receiving placebo. With this result, nicotinamide's future as a significant therapy in type 1 diabetes is in doubt.

There is one recent single-blind, placebo-controlled study indicating that nicotinamide improves insulin secretion and metabolic control in lean type 2 diabetic patients with secondary failure to sulfonylureas. Follow-up is needed.

Recently nicotinamide reversed neurological and neurovascular deficits in streptozotocin diabetic rats, leading the researchers to conclude that nicotinamide "deserves consideration as an attractive, nontoxic therapy for the treatment of diabetic peripheral neuropathy." Other research adds further evidence that nicotinamide may be a significant neuroprotectant in a number of contexts. High-dose nicotinamide prevented oxidative mitochondrial dysfunction in a cellular model and improved motor deficit in a *Drosphilia* model of Parkinson's disease. It has also shown to have a broad range of neuroprotective effects in some mouse models of chemically induced Parkinsonism. In still other tests, nicotinamide has exerted protective effects in animal models of traumatic brain injury and ischemia, including reduced infarct size and improved functional recovery. Acute neuroprotection and edema reductions were achieved in one such recent study. A number of acute pathophysiological processes were said to be favorably modulated by nicotinamide in this study, indicating, among other things, that the agent can inhibit cortical neuronal death.

In another recent study, nicotinamide demonstrated potent antiinflammatory activity, inhibiting various proinflammatory cytokines. These *in vitro* results encouraged the researchers to speculate that nicotinamide might have some future role in the treatment of human inflammatory diseases.

Nicotinamide suppressed hyperphosphatemia in hemodialysis patients. Hyperphosphatemia is a considerable problem in hemodialysis, and the available remedies are often toxic in the long term. Thus, the observation that nicotinamide inhibits sodium-dependent phosphate transport in rat renal tubule and small intestine encouraged researchers to recently examine whether nicotinamide could reduce serum levels of phosphorous and intact parathyroid hormone in patients undergoing hemodialysis. Mean dose of nicotinamide in this study was 1,080 milligrams per day for 12 weeks. Beneficial effects were sufficient for the researchers to conclude: "Nicotinamide may provide an alternative for controlling hyperphosphatemia and hyperparathyroidism without inducing hypercalcemia in hemodialysis patients."

Also recently, researchers reported that a niacinamide (nicotinamide) moisturizing cream reduced facial hyperpigmentation compared with a control vehicle, in Asian women. A significant lightening of skin was noted after four weeks of treatment and was attributed to an inhibition of melanosome transfer from melanocytes to keratinocytes. More research is needed to further explore this finding. There is a case study showing pronounced improvement in a patient with generalized granuloma annulare treated with high-dose (1,500 milligrams daily) niacinamide for six months. This patient's disease had previously resisted treatment with topical adrenal steroids, oral erythromycin and oral zinc.

A recent double-blind, placebo-controlled, pilot study examined the effect of nicotinamide in subjects with osteoarthritis. In the study, 72 subjects with osteoarthritis were randomly assigned to receive nicotinamide (500 milligrams six times per day) or placebo. The study lasted 12 weeks. Subjects who received nicotinamide reduced their non-steroidal anti-inflammatory (NSAID) medication by 13% compared with those in the placebo group. Pain levels were no different in the two groups. Nicotinamide reduced the sedimentation rate by 22% and increased joint mobility by 22% over controls. Follow-up is needed.

Some preliminary evidence suggests that nicotinamide may increase the irradiation response of experimental tumors. More research is needed in this area.

Nicotinamide produced effects no better than placebo when used in a double-blind trial involving 48 subjects with tinnitus.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Nicotinamide is contraindicated in those hypersensitive to any component of a nicotinamide-containing preparation.

High-dose nicotinamide (doses greater than 500 milligrams/day) is contraindicated in those with liver disease and in those with active peptic ulcer disease.

PRECAUTIONS

Pregnant women and nursing mothers should avoid supplemental doses of nicotinamide greater than the U.S. RDA (20 milligrams/day), unless higher doses are prescribed by their physicians.

The use of nicotinamide for any medical indication requires medical supervision.

Those with a history of peptic ulcer disease, gastritis, liver disease, gallbladder disease, diabetes and gout, should exercise caution in the use of high-dose nicotinamide.

ADVERSE REACTIONS

In contrast to nicotinic acid, nicotinamide does not cause flushing and has only very rarely been associated with diabetogenic effects. There are rare reports of elevations in liver tests and liver damage, including jaundice and parenchymal liver cell injury. These reports were in those using very high doses of nicotinamide (10 grams or greater, daily).

Adverse reactions in those using high-dose nicotinamide, include nausea, vomiting, diarrhea, headache and dizziness.

INTERACTIONS

DRUGS

Carbamazepine: Concomitant use of nicotinamide and carbamazepine may decrease carbamazepine clearance.

OVERDOSAGE

Nicotinamide overdosage is not reported in the literature.

DOSAGE AND ADMINISTRATION

Nicotinamide is the form of niacin which is typically used for nutritional supplementation. It is also the form of niacin used in food fortification. It is available as a single ingredient product (immediate-release and sustained-release) and in multivitamin and multivitamin/multimineral products. Typical supplemental dosage ranges from 20 to 100 milligrams daily. Pre- and postnatal vitamin/mineral supplements typically deliver a dose of 20 milligrams daily.

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Nobiletin

DESCRIPTION

Nobiletin is a member of the polymethoxyflavone family of flavones. Flavones themselves comprise a subclass of the large class of plant substances, the flavonoids. Polymethoxylated flavones (PMFs) exist almost exclusively in the *Citrus* genus, particularly in the peels and tissues of sweet oranges (*Citrus sinensis*), the peels and tissues of bitter oranges (*Citrus aurantium* L.) and, especially, the peels and tissues of tangerines *(Citrus reticulata* Blanco), including Dancy and Cleopatra tangerines and clementines. The two most common PMFs found in citrus peels are nobiletin and tangeretin (see Tangeretin). Sinensetin is the third most common PMF found in the peels and tissues of citrus fruits.

Nobiletin, like other flavonoids, is a plant secondary metabolite. Plant secondary metabolites comprise the defense system of plants against fungi, predators and pests, among other things. Mal seco is a fungal disease of citrus varieties, mainly lemons, caused by the pathogenic fungus *Deuterophoma tracheiphila* (or *Phoma tracheiphila)* and is widespread throughout the Mediterranean region. There is almost no nobiletin in lemons. Nobiletin, when inoculated in lemon seedlings infected with the mal seco fungus, was demonstrated to have strong fungistatic activity. Tangeretin was found to be weakly active. Nobiletin-containing citrus fruits are quite resistant to mal seco. Lemons (*Citrus limon*) and grapefruits (*Citrus paradisi*) are virtually devoid of nobiletin and other PMFs.

Recently, there has been great interest in studying nobiletin for its possible anti-inflammatory, anticarcinogenic, antiatherogenic and neuroprotective activities. It turns out that nobiletin and other PMFs appear to have greater oral bioavailability than their polyphenolic cousins.

Nobiletin is chemically described as 5,6,7,8-tetramethoxy-2-(3,4-dimethoxyphenyl)-4H-1-benzopyran-4-one. Nobiletin is also known as 3′,4′,5,6,7,8-hexamethoxyflavone, and 5,6,7,8,3′,4′-hexamethoxyflavone. Its empirical formula is $C_{21}H_{22}O_8$ and its molecular weight is 402,39. The chemical structures below are described within this monograph.