

Niacin: Nicotinic Acid and Nicotinamide

Function

The term “niacin” may refer either specifically to nicotinic acid or to the total amount of nicotinic acid and nicotinamide in the diet (Food and Nutrition Board 1998). The biological requirements for this vitamin may be met by intakes of nicotinic acid or nicotinamide and (if protein intakes are sufficient) by the biological conversion of the amino acid tryptophan to nicotinic acid. Thus, an individual’s niacin requirements depend on the amount and quality of dietary protein intake (Cervantes-Laurean et al. 1999). Niacin has fundamental roles as part of reduction/oxidation coenzymes involved in energy metabolism, amino acid metabolism, and detoxification reactions for drugs and other substances.

Nicotinic acid at an intake of 1,000 mg or higher is an effective antihyperlipidemic agent (Witztum and Steinberg 1996). It is particularly effective in lowering the blood concentrations of low- and very low-density lipoprotein (LDL and VLDL) cholesterol and in increasing the concentration of high-density lipoprotein (HDL) cholesterol. Intakes at quantities of one gram or more, however, not only provide pharmacological benefits but also carry significant risk of adverse effect, thus requiring medical supervision and monitoring. High intakes of nicotinic acid produce a vasodilative effect that can result in an intense itching or burning sensation of the skin, especially on the face and neck. This skin-flushing reaction usually persists for only a few doses. The daily dose is generally administered in three doses, and each is increased gradually until the desired total dose is achieved. Liver function tests and tests for uric acid, fasting blood glucose, and lipid levels should be conducted. Adverse reactions may require decreased dosage or discontinuation in favor of other agents. The flushing reaction may be substantially avoided through use of a slow-release preparation of nicotinic acid. Such preparations carry greater risk of liver toxicity, although they may also provide greater pharmacological benefit at any given dose (Rader et al. 1992).

Nicotinamide, or niacinamide, performs all the essential biochemical functions of niacin and prevents niacin deficiency. Large doses of nicotinamide do not cause vasodilation or flushing and do not lower serum lipid concentrations. Large doses of nicotinamide improve islet-cell regeneration in tissue culture, and this effect could have a protective action on residual insulin secretion in insulin-dependent (Type 1) diabetes mellitus (IDDM) patients (Cervantes-Laurean et al. 1999). Thus, nicotinamide might have a place in IDDM therapy.

Safety Evidence

The skin-flushing reaction produced by nicotinic acid has been recognized for more than half a century (Bean 1978). When taken on an empty stomach, crystalline nicotinic acid in doses as small as 10 mg may produce a mild and transient, but noticeable, flushing reaction. While not desirable, such reactions produce no known adverse consequences, and they are seldom perceptible when small amounts of nicotinic acid are taken in tablet or capsule form or consumed with food.

Serious side effects of nicotinic acid have occasionally occurred when gram quantities were taken to lower serum lipids (Rader et al. 1992). Liver toxicity and serious gastrointestinal effects can sometimes occur in persons consuming a gram or more per day of nicotinic acid. Gastrointestinal side effects may include indigestion, nausea, vomiting, and diarrhea, and, in some persons, may necessitate discontinuation of nicotinic acid intake. Liver toxicity is most commonly monitored by increases in serum transaminase enzymes of liver origin released by damage to liver cells. Small increases in serum concentrations of transaminases do not indicate significant liver damage and return to normal after cessation of nicotinic acid intake. More severe reactions may produce jaundice, fatigue, and, in at least one case, fulminant liver failure (Clementz and Holmes 1989).

There is a strong correspondence between the minimum adverse effect level identified through clinical trials and that suggested by the published anecdotal case reports. Many severe reactions to nicotinic acid, especially liver toxicity, have involved ill-advised or inadvertent switching from unmodified nicotinic acid preparations to slow-release formulations (Rader et al. 1992). Most reported adverse reactions to nicotinic acid have occurred with intakes of 2,000 to 6,000 mg per day. There are only two anecdotal cases reported where intake levels were below 1,000 mg: one for slow-release nicotinic acid at 500 mg per day, and one for unmodified nicotinic acid at 750 mg per day (Rader et al. 1992). The clinical trial of McKenney and colleagues (McKenney et al. 1994) used two groups of adult subjects, studying one for immediate-release nicotinic acid and one for slow-release nicotinic acid. These two groups were observed for six weeks at dosage levels of 500, 1,000, 1,500, 2,000, and 3,000 mg per day. The data showed no adverse reactions at 500 mg per day for either form of nicotinic acid, but statistically did show significant effects beginning at 1,000 mg per day (gastrointestinal effects for unmodified nicotinic acid, and mild liver toxicity for slow-release nicotinic acid). Gram quantities of nicotinic acid should not be self-administered as a dietary supplement but may be safely used under the care and monitoring of a physician. Such application, it should be noted, is a pharmaceutical use, not a dietary supplement use.

Published Official Reviews of Niacin Safety

As concluded by FNB, at sufficient dosage levels nicotinic acid, but not nicotinamide, causes vasodilation and skin-flushing (Food and Nutrition Board 1998). Unfortunately, FNB established a LOAEL based on skin-flushing by nicotinic acid, selected a UF value, and applied the derived UL value to both nicotinic acid and nicotinamide. The FNB has implicitly judged the flushing reaction to qualify as a “hazard” and therefore a proper basis for a UL, principally because of the undesirability of the effect rather than any evidence of actual harm. This nuisance caused by nicotinic acid was clearly illustrated when an excessive amount accidentally added to bagel dough resulted in uncomfortable and alarming effects that were completely unexpected by the several persons who experienced them (Centers for Disease Control 1983).

The LOAEL identified by FNB was 50 mg, based on the clinical studies by Sebrell and Butler (1938) and Spies et al. (1938). Because of the mild and transient nature of the flushing effect, FNB justified a UF of 1.5 to apply to the LOAEL, leading to determination of a UL of 35 mg. It is noteworthy that the clinical studies from which FNB derived the UL value involved bolus doses of nicotinic acid administered to subjects with empty stomachs and no previous regular exposure to dosed nicotinic acid.

The EC SCF recognized that the more severe forms of toxicity of nicotinic acid occur at doses greater than 500 mg (Scientific Committee on Food 2002), but identified a LOAEL of 30 mg, based on the skin-flushing reaction in the same studies (i.e., Sebrell and Butler 1938 and Spies et al. 1938) relied upon by FNB. The EC SCF selected a UF of 3 and therefore derived a UL of 10 mg for nicotinic acid (Scientific Committee on Food 2002). The EC SCF attempted to justify its identification of the vasodilatory (flushing) effects as the critical adverse effect endpoint (that is, as the *hazard* of concern in the UL risk assessment model) based not only on the nuisance of discomfort but also on the purely hypothetical possibility of exaggeration of positional hypotension and related increased risk of falls, which are a common cause of morbidity and mortality in the elderly (Scientific Committee on Food 2002). This possibility seems to be nothing more than conjecture, and no evidence is offered to support it.

For nicotinamide, EC SCF identified a UL of 900 mg (Scientific Committee on Food 2002).

The UK EVM concluded that “there are insufficient data from human or animal studies to establish a safe upper level for nicotinic acid” (Expert Group on Vitamins and Minerals 2003). Nonetheless, UK EVM set a GL for nicotinic acid based on UL methodology. In agreement with FNB on a LOAEL of 50 mg

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(based on Sebrell and Butler 1938 and Spies et al. 1938) and with EC SCF on a UF of 3, UK EVM derived a unique GL of 17 mg for nicotinic acid.

Like EC SCF, UK EVM established a safe level for nicotinamide distinct from that for nicotinic acid (Expert Group on Vitamins and Minerals 2003). It identified no adverse effects for nicotinamide at intakes of 25 mg per kg (Pozzili et al. 1995) and 42 mg per kg (Lampeter et al. 1998), but judged the database small enough to justify a UF of 3. The derived GL for a 60 kg person is 500 mg of supplemental nicotinic acid per day. Assuming a food intake of not more than 57 mg from foods, UK EVM identified 560 mg per day as the GL for total intake from all sources.

CRN ULS for Nicotinic Acid

(based on hepatotoxic effects)

With its transient and non-pathological effects, the flushing reaction in response to supplemental nicotinic acid deserves to be characterized as a *nuisance*, but not as a *hazard*. When high intakes result from supplementation, appropriate product labeling can alert the consumer of this nuisance effect. Thus, flushing does not qualify as a hazard for supplemental intake of nicotinic acid. The CRN ULS for supplemental nicotinic acid is based on the hepatotoxic effects at much higher doses, effects that can be clearly hazardous.

There are only two anecdotal cases of reported hepatotoxic effects at intakes of less than 1,000 mg per day, and many uncertainties exist in these cases regarding the amount consumed as well as the presence or absence of preexisting or confounding conditions such as alcoholism or other compromises of liver function. The clinical trial data (McKenney et al. 1994) are appropriate to identify a NOAEL of 500 mg per day and a LOAEL of 1,000 mg per day for liver or gastrointestinal effects. It should be noted, however, that the adverse reactions to 1,000 mg of unmodified nicotinic acid were mainly gastrointestinal effects, which generally have less potential for serious outcomes than the liver toxicity that results in some persons who consume 1,000 mg per day of slow-release nicotinic acid. Additionally, gastrointestinal effects seem much more likely to be self-limiting due to consumer awareness and likely self-correction. These differences warrant advising a lower limit for slow-release nicotinic acid than for the unmodified form, and the twofold decreases in the NOAEL and LOAEL for slow-release nicotinic acid seem ample, based on case reports (Rader et al. 1992) and clinical trial results (McKenney et al. 1994). Thus, for slow-release nicotinic acid the NOAEL is 250 mg, and the LOAEL is 500 mg.

The reports by FNB, EC SCF, and UK EVM did not set NOAEL or LOAEL values based on the hepatotoxic effects of nicotinic acid. Those reviews

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identified intakes of about 3 g as the levels at which such effects occur with substantial frequency. None of these reports addressed slow-release nicotinic acid preparations in any detail.

CRN identifies the following LOAEL and NOAEL values for nicotinic acid supplements:

Immediate-release nicotinic acid formulations

LOAEL, based on hepatotoxicity	1,000 mg
NOAEL, based on hepatotoxicity	500 mg
Flush label warning	greater than 35 mg

Slow-release nicotinic acid formulations

LOAEL	500 mg
NOAEL	250 mg
Flush label warning	None; not needed

Considering the infrequent effects at the LOAEL levels of intake and the reversible nature of mild, short-term hepatotoxicity, the NOAEL values are identified as the CRN ULS values, provided that immediate-release formulations carry appropriate labeling about flushing. Thus, the CRN ULS values for nicotinic acid supplements are:

Immediate-release nicotinic acid supplements

CRN ULS = 500 mg
(contingent upon proper label statements about flushing)

Slow-release nicotinic acid supplements

CRN ULS = 250 mg

Comparison of Safety Values for Nicotinic Acid

CRN ULS, immediate-release	500 mg (based on liver effects)
CRN ULS, slow-release	250 mg (based on liver effects)
CRN threshold for flush label warning	35 mg
US FNB UL	35 mg* (based on flushing effects)
EC SCF UL	10 mg (based on flushing effects)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	17 mg (based on flushing effects)

* This UL for nicotinic acid is applied to the total of all forms of niacin.

CRN ULS for Nicotinamide

There is much less information on nicotinamide than there is for nicotinic acid, but there also appears to be much less use at high levels of intake. Clinical trials on high-dose nicotinamide have been small. One study observed no adverse effects in sixteen subjects who received 3,000 mg nicotinamide per day (Vague et al. 1987), but the method of monitoring for such effects was not specified. Other studies that describe monitoring methods in more detail have found no adverse effects for nicotinamide intakes in the range of 1,000 to 2,900 mg per day (Mendola et al. 1989; Chase et al. 1990; Pozzilli et al. 1995; Lampeter et al. 1998). Nicotinamide intakes of more than 3,000 mg per day have resulted in adverse gastrointestinal and liver effects (Rader et al. 1992).

The clinical trial results support a very confident NOAEL of 25 mg per kg per day. Because some of these trials were performed with subjects younger than eighteen years old who had lower than fully adult body weights, 60 kg was used to calculate a NOAEL of 1,500 mg per day. The absence of adverse effects in clinical trials that included nicotinamide dosages of up to 3,000 mg per day reduces the uncertainty in this value.

Comparison of Safety Values for Nicotinamide

CRN ULS	1,500 mg
US FNB UL, total intake	35 mg*
EC SCF UL, total intake	900 mg
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	500 mg (560 mg total)

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* This UL for nicotinic acid is applied to the total of all forms of niacin.

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