Vitamin B_3

Common Acronyms

bw	body weight
CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
FSSAI	Food Safety and Standards Authority of India
IOM	Institute of Medicine
IU	international unit
LOAEL	lowest observed adverse effect level
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NIH	National Institute of Health
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
ROK	Republic of Korea
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

Introduction

Niacin (i.e., the first identified vitamin B3 compound) is a precursor to nicotinamide adenine dinucleotide (NAD), the reduction/oxidation coenzyme involved in energy metabolism, amino acid metabolism, and detoxification reactions for drugs and other substances. All tissues in the body convert absorbed vitamin B3 compounds into NAD, which is then converted into nicotinamide adenine dinucleotide phosphate (NADP) (NIH, 2022). Vitamin B3 comes in several unique forms, which were previously all categorized as niacin: (1) nicotinic acid, which is often used interchangeably with “niacin” (pyridine-3- carboxylic acid), (2) nicotinamide (nicotinic acid amide, niacinamide), (3) nicotinamide riboside [NR], and (4) other derivatives

(e.g., inositol hexanicotinate [IHN]) "that exhibit the biological activity of nicotinamide" (IOM 1998; Burgeois et al. 2006; Delage 2017). Other derivatives of vitamin B3 may be converted to nicotinic acid or may contain nicotinic acid, nicotinamide, or their releasable moieties; whether these compounds should be referred to as *niacin* depends on the biological effects that are attributed to them, the interpretation of the evidence for the rates of uptake and metabolism, and the release of the chemical components (apparent bioavailability) that produce biological effects similar to the primary forms of niacin (Delage 2017).

Several forms of "vitamin B3" are marketed in the United States as dietary supplements, including:

- nicotinic acid (unmodified, immediate release),
- nicotinic acid (extended-release) forms that contain acid and an agent to slow the release (e.g., wax matrix, ion exchange gel),
- nicotinamide,
- nicotinamide riboside (NR) (including its chloride and malate salt forms), and
- inositol hexanicotinate (IHN).[1]

Niacin is an essential water-soluble vitamin; thus, excess is not stored in the body but is metabolized and excreted; therefore, supplemental niacin or other forms of vitamin B3 must be ingested daily (Delage 2017). Niacin can also be generated endogenously from the biological conversion of the amino acid tryptophan to nicotinic acid, having a niacin equivalent of 60, meaning 60 mg of tryptophan is required to make 1 mg of niacin. Thus, an individual's niacin level depends on the amount and quality of that person's dietary protein intake (Cervantes-Laurean et al. 1999). The bioavailability and safety considerations of each of these dietary supplement forms are considered separately relative to their respective supplemental UL values for adults.

[1] Published clinical trials were identified for nicotinamide mononucleotide (NMN), a "niacin like" compound available as a dietary supplement: however, this form was not reviewed in detail because it is not marketed or labeled as a source of niacin (NIH 2022).

Bioavailability

Nicotinic Acid

Intestinal uptakes of free nicotinic acid are rapid and nearly total; that is, single large doses of up to 3,000 to 4,000 mg per day of nicotinic acid are almost completely absorbed by adults (Bechgaard and Jespersen 1977; IOM 1998). At low concentrations, absorption occurs via sodium-dependent facilitated diffusion with passive diffusion becoming the dominant route at increased concentrations (IOM, 1998). Once absorbed by the gut, up to 30 percent of the plasma nicotinic acid is bound to plasma protein. Nutritional functions related to niacin-dependent coenzymes occur at low intake levels (15 to 18 mg per day), whereas the skin flushing effect (see below), which is a nuisance but not considered to be a *true hazard* according to CRN's methodology, becomes noticeable when intakes exceed 50 mg per day (Spies et al. 1938).

Extended-Release Nicotinic Acid

Extended-release nicotinic acid has been investigated for potential beneficial effects on serum lipids while minimizing or avoiding the flushing effect of nicotinic acid (Norris 2006). For extended-release nicotinic acid, the potential beneficial impacts on serum lipid concentrations are directly related to the release of the nicotinic acid from the matrix in which it is presented. Thus, the uptake of nicotinic acid from extended-release nicotinic acid formulations is dependent on the specific delivery matrix and is significantly slower than that of free nicotinic acid, but rapid enough to achieve effective plasma nicotinic acid concentrations (Aronov et al. 1996; Menon et al. 2007).

Nicotinamide

Nicotinamide has been shown to perform the essential biochemical functions of niacin, albeit its pathway into the cell and formation of intracellular NAD+ is different. Similar to niacin, the oral absorption of nicotinamide occurs in the stomach and intestine with higher concentrations resulting in a shift from sodium ion-dependent facilitated diffusion to passive diffusion as the predominant route of absorption (IOM, 1998). Escalating oral doses of 3,000, 4,000, 5,000,

6,000, and 10,000 mg of nicotinamide showed a linear relationship between maximum recorded plasma concentrations and the dose in milligrams. Maximum plasma levels were observed after 30 minutes of intake in most patients consuming up to 6,000 mg of nicotinamide. Doses up to 6,000 mg were reported by the authors to be well tolerated and resulted in average maximum recorded plasma levels (mean ± 1 SEM) of 156.4 ± 33.6 µg per ml. Doses of 10,000 mg were generally not well tolerated, but a high plasma level was maintained on average for at least 4 hours (Dragovic 1995).

Nicotinamide Riboside (NR)

Similar to nicotinamide, nicotinamide riboside (NR) is an endogenous compound that follows the salvage pathway to form NAD, intracellularly. From available toxicokinetic data in mice, rats, dogs, and humans, a portion of NR is likely absorbed as nicotinic acid and nicotinamide following metabolism in the gut (EFSA 2019; Trammel et al. 2016). NR is a source from which nicotinamide is bioavailable, and based upon its structure and size, the molecular equivalent of, e.g., 1 mg NR chloride is equal to 0.42 mg nicotinamide per kg bw per day (EFSA 2019). Although NR has been proposed to serve primarily as a source of nicotinamide in some studies, genetic models strongly implicate NR as a direct NAD+ precursor (Diguet et al, 2018; Frederick et al., 2016).

Inositol Hexanicotinate (IHN)

In 2009, the EFSA Scientific Panel on Food Additives and Nutrient Sources Added to Food concluded that nicotinate from IHN is a bioavailable source of niacin (EFSA 2009). IHN, like extended-release nicotinic acid, has been investigated for potential beneficial effects on serum lipids while minimizing the flushing effect (Norris 2006). The available data suggest that intestinal absorption of IHN varies widely, with an average of 70 percent of the administered dose being absorbed into the bloodstream (Harthorn and Lindqvist 1964). However, the majority of IHN that is absorbed appears to remain intact after absorption.

Metabolism of IHN to release free nicotinic acid can result in the physiological functions of nicotinic acid, depending on the dose, rate, and amount of release. Humans given oral doses of IHN obtain

peak, but very low, levels of plasma free nicotinic acid at 6 to 12 hours (Welsh and Ede 1961; Sommer 1965), whereas oral doses of nicotinic acid result in peak plasma levels of nicotinic acid at 0.5 to 1 hours (Carlson et al. 1968). The peak plasma levels of nicotinic acid after oral doses of IHN are dramatically lower compared with oral doses of nicotinic acid.

Safety Considerations

Nicotinic Acid and Extended-Release Nicotinic Acid

Nicotinic acid can produce a variety of adverse effects, depending on the intake and health of the consumer. Clinically relevant doses of nicotinic acid can produce a vasodilative effect that results in an itching or burning sensation of the skin, especially on the face and neck. The skin flushing reaction produced by nicotinic acid is well recognized (Bean 1978) and is mediated by activation of the G protein-coupled receptor 109A (GPR109A) increasing arachidonic acid and prostaglandin release in dermal cells, resulting in vasodilation (Benyó 2006). When taken on an empty stomach, nicotinic acid in doses as small as 10 mg/day may produce a mild and transient, but noticeable, flushing reaction. While not desirable, such reactions produce no known adverse consequences, and they are almost never perceptible when small amounts of nicotinic acid are taken in tablet or capsule form or consumed as part of food. Therefore, this flushing effect is considered to be a *nuisance effect*, rather than a *true hazard*, according to CRN's methodology. This flushing reaction usually persists for only a few doses and may be reduced by splitting the daily dose into three parts, each increased gradually until the desired total dose is achieved or by using an "extended- release" preparation of nicotinic acid; however, such preparations carry greater risk of liver toxicity (Rader et al. 1992).

Nicotinic acid at an intake of 1,000 mg per day or higher is an effective dyslipidemic agent with a broad spectrum of effects, including increasing high-density lipoprotein (HDL) cholesterol, reducing low- density lipoprotein (LDL) cholesterol, high lipoprotein(a), and triglycerides (Witztum and Steinberg 1996; Carlson 2005). However, intakes of quantities of >1,000 mg/day can produce a variety of effects, ranging from nuisance effects (i.e., flushing) to serious illness. Gastrointestinal side effects may include indigestion, nausea, vomiting, and diarrhea and, in some people, may necessitate discontinuation of nicotinic acid supplements. More serious side effects

impacting the liver or intestines have been reported with pharmacologic doses (e.g., 1,000 mg per day) taken for dyslipidemia. Liver toxicity clinically presents as 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 levels 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 1987; Rader et al. 1992).

There is a strong correspondence between the minimum adverse effect level identified through clinical trials and that suggested by published anecdotal case reports. Many severe reactions to nicotinic acid, especially liver toxicity, have involved ill-advised, uninformed, or inadvertent switching from unmodified nicotinic acid preparations to extended-release formulations (Rader et al. 1992; MacKay et al. 2012). Most reported adverse reactions to nicotinic acid have occurred with intakes of 2,000 to 6,000 mg of nicotinic acid per day in both immediate-release and extended-release forms. There are two anecdotal cases reported in which intake levels were below 1,000 mg per day: one for extended-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 et al. (1994) studied two groups of adult subjects, one for immediate-release nicotinic acid and one for slow-release (or extended-release) nicotinic acid. These two groups were observed for 6 weeks at dosage levels of 0, 500, 1,000, 1,500, 2,000, or 3,000 mg per day. The data showed no adverse reactions at 500 mg per day for either form of nicotinic acid. Statistically significant effects beginning at 1,000 mg per day were observed, including gastrointestinal effects for immediate-release nicotinic acid, and mild liver toxicity (i.e., significant increase of mean liver aminotransferase and alkaline phosphatase levels) for extended-release nicotinic acid. More recently, Javadian and colleagues (2024) performed a randomized controlled clinical trial with immediate-release nicotinic acid (0 or 600 mg per day) for 8 weeks in patients on maintenance hemodialysis. Javadian et al. reported no significant changes in a variety of clinical chemistry endpoints, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and no significant difference in reported side effects between treated and control groups.

Grundy et al. (2002) studied extended-release nicotinic acid (the FDA-approved product,

Niaspan) to control dyslipidemia in patients with type II diabetes. In this well-designed but modestly sized clinical trial, groups with 0, 1,000, or 1,500 mg per day were assessed for clinical benefits and monitored for adverse effects. Rates of adverse events other than flushing were similar for the niacin and placebo groups. No hepatotoxic effects or myopathy were observed. Since this trial involved patients with type II diabetes, application to the general population is not certain. In a more recent randomized, controlled cross over study, extended-release nicotinic acid at 1,000 mg per day alone or in combination with 20 mg of laropiprant for seven days was used to examine its benefits on endothelial function in individuals with low HDL cholesterol (Figueiredo et al. 2014). The study reported mild to moderate flushing in 22% of the patients in both arms, but no other adverse effects were reported. While flushing was reported in patients, the significance of the incidence was not reported given the lack of a placebo control group in the study. Of note, parameters relevant to potential liver effects (e.g., liver enzyme levels) were not assessed in this study.

One recent study looked at various terminal metabolites of niacin in cardiac patients as part of a prospective discovery cohort and concluded an association between serum levels of some metabolites (N1-methyl-2-pyridone-5-carboxamide (2PY) and N1-methyl-4-pyridone-3-carboxamide (4PY)) and residual cardiovascular disease risk (Ferrell et al. 2024). However, numerous publications argue that the results of the Ferrell et al. study should be interpreted with caution for various reasons; for example, that the mechanism suggested by the authors as leading to a potential adverse cardiovascular outcome has, conversely, been shown in other studies to be abated by niacin (Schreiber et al. 2024; Guyton and Boden 2024). In addition, numerous studies have been published demonstrating either no significant association or a reduced risk of cardiovascular mortality associated with niacin intake (e.g., Fu et al. 2024; Lin et al. 2024: Yang et al. 2024).

Nicotinamide

The volume of available clinical trial data on nicotinamide has increased since the 3rd edition, supplementing the previously identified studies that found no adverse effects for nicotinamide at intakes ranging from 1,000 to 1,500 mg per day (Mendola et al. 1989; Pozzilli et al 1995). Most of the subsequent published studies were performed at doses below the NOAEL value which

served as the basis for the previously derived CRN supplemental UL of 1,500 mg per day and reported no significant differences in adverse effects from control groups following intervention with nicotinamide (Allen et al. 2023; Chen et al. 2015; Chen et al. 2016; Damien et al. 2017; DeBoer et al. 2021; Hajdenberg 2016; Kohli et al. 2023). Two studies with higher nicotinamide levels (1,500 and 1,800 mg per day) reported no serious adverse effects (Hui et al. 2020; El Ters et al. 2020). Hui et al. (2020) performed a double blind, randomized, cross over clinical trial for nicotinamide in patients with glaucoma. Individuals were given placebo or 1,500 mg per day of nicotinamide for six weeks followed by 3,000 mg per day for an additional 6 weeks. No serious adverse effects were reported; side effects were limited to nausea and headaches in the intervention group. In another randomized, double-blind, placebo-controlled clinical trial, patients with autosomal dominant polycystic kidney disease were given 1,800 mg per day (30 mg per kg per day at 60-kg bw) for 12 months. None of the adverse events reported differed in frequency between the placebo and treatment group (El Ters et al. 2020).

Only a few clinical trials on high-dose nicotinamide (i.e., >3,000 mg per day) are available. One study observed no adverse effects in 16 subjects who received 3,000 mg of nicotinamide per day (Vague et al. 1987), but the method of monitoring for such effects was not specified. However, other studies of nicotinamide intakes of more than 3,000 mg per day have resulted in adverse gastrointestinal (e.g., nausea and vomiting) and liver effects (e.g., increased AST, ALT bilirubin, fibrosis in the liver) (Rader et al. 1992). In an exploratory, open-label, dose-escalation study to assess the safety of high-dose nicotinamide in patients with Friedreich's ataxia, patients were given daily doses of 3,000 to 8,000 mg per day for eight weeks (Libri et al. 2014). The primary reported side effect was mild, reversible nausea staring at 4,000 mg per day. Other effects reported include headache, lightheadedness, vomiting, hypersomnia, fatigue, and diarrhea; incidence of effects began at 3,000 mg per day and increased with increasing dose. In addition, increases in abnormal results from liver function tests occurred in 3 out of 10 patients when taking 8,000 mg per day and all resolved with reduction of nicotinamide dose. Nicotinamide was not reported to cause a flushing reaction in the studies reviewed.

Nicotinamide Riboside (NR)

NR was not assessed in the 3rd edition of this chapter; however, the literature search conducted as

part of this update did not identify any human clinical trials published prior to 2014 that met the inclusion criteria. Numerous clinical studies have been published on NR since the 3rd edition. All identified studies used the chloride salt form of NR; therefore, NR and its chloride salt form are used interchangeably throughout the chapter. None of the identified studies reported any serious adverse effects. Most studies reported no adverse effects related to intervention with NR up to 1,000 mg per day for durations ranging from 3 weeks to 6 months (Airhart et al. 2017; Ahmadi et al. 2023; Bhandari et al. 2025; Brakedal et al. 2022; Elhassan et al. 2019; McDermott et al. 2024; Remie et al. 2020; Vreones et al. 2023; Wu et al. 2025).[2] Six studies identified some nuisance effects following administration of 500 to 3,000 mg per day of NR (Dollerup et al. 2018; Martens et al. 2018; Wang et al. 2022; Berven et al. 2023; Lapatto et al. 2023; Presterud et al. 2024). Nuisance effects were reported in a small open label, observational intervention trial with individuals with ataxia telangiectasia (Presterud et al. 2024). NR was administered at an initial dose of 150 mg per day for two weeks and titrated up to 500 mg per day for a total of 18 months of supplementation (ten total participants; seven children and three adults). The authors reported no severe adverse effects were observed following dosing of NR (and additional monitoring for a total of two years) and that NR use was well tolerated outside of some reported nuisance effects (e.g., loose stools in one participant and transient mild stomach discomfort in one participant). In another randomized, controlled clinical trial in healthy individuals, 1,000 mg NR (500 mg twice daily) for six weeks was reported to be well tolerated with no serious adverse effects (Martens et al. 2018). Nuisance effects were reported, including nausea, flushing, leg cramps, and increased bruising in the NR treatment group and headache, skin rash, flushing, fainting, and drowsiness were reported in the placebo group.[3] A clinical study conducted in twenty twin pairs reported that NR supplementation at an initial dose of 250 mg per week and titrated up daily to a final dose of 1,000 mg per day for a minimum of four months was well tolerated by all participants (Lapatto et al. 2023). There were no clinically significant changes in hematology or clinical chemistry parameters measured in this study; side effects included muscle pain, gastrointestinal irritation, sweating, nausea, and headache in the NR group. Dollerup et al. (2018) performed a randomized placebo-controlled clinical trial in healthy, obese Caucasian men. Administration of placebo or 2,000 mg NR per day (1,000 mg twice daily) was stated by the authors to be well tolerated, and only minor adverse nuisance effects were reported

[2] Any adverse events observed were determined not to be related to NR. Vreones et al. (2023) did not report on side effects or adverse events.

[3] While statistics were not performed on these effects between groups, only one individual in the NR treatment group reported flushing effects versus two individuals in the placebo group.

in the NR group, including flushing, excessive sweating, bloating and transient changes in stool. Another randomized placebo-controlled trial administered NR or placebo starting with 500 mg per day (250 mg twice daily) and titrating up to 2,000 mg per day per during week three, for a total study duration of twelve weeks (Wang et al. 2022). There were no between group differences in adverse events or laboratory parameters (clinical chemistry and hematology) assessed in this study conducted in heart failure patients with reduced ejection fraction.[4] Berven et al. (2023) conducted a small randomized, double-blind, placebo-controlled trial designed to "provide initial evidence of safety and tolerability for NR at a dose of 3000mg daily." In this study, groups of ten individuals with Parkinson's Disease received placebo or 3,000 mg NR daily for four weeks. All adverse effects in this study were determined to be mild, with no significant differences in frequency between groups.

Inositol Hexanicotinate (IHN)

Several clinical studies have demonstrated that IHN may have a beneficial effect on endothelium-dependent vasodilatation. The clinical research literature includes several positive studies on the use of IHN for improving blood flow in conditions where blood flow is compromised (Ring and Bacon 1977; Head 1986; O'Hara et al. 1988). IHN does not cause a flushing reaction and clinical trials using IHN up to 4,000 mg daily for 3 months do not demonstrate adverse effects (Sunderland et al. 1988; Head 1996). These clinical trials have not been designed to assess the safety of IHN; however, no meaningful adverse effects have been noted in several well-designed clinical trials using IHN in amounts that range from 600 to 4,000 mg daily.

Official Reviews

IOM (1998). The 1998 IOM report is limited to evidence concerning intake of niacin from supplements, stating "there is no evidence of adverse effects from the consumption of naturally occurring niacin in foods." In addition, the IOM reported that the flushing reaction is an "adverse effect" for nicotinic acid, and therefore an appropriate basis for a UL, principally

[4] Patients in this study were taking at least one concomitant medication. Given the relatively small number of studies identified for NR (as a newer form of vitamin B3), CRN's inclusion criteria were modified for this chapter to include all studies that administered NR orally in adults for a minimum of one week. See Methods Chapter for additional details.

because of the undesirability of the effect rather than any evidence of actual harm. The LOAEL identified by the IOM was 50 mg per day, based on clinical studies by Sebrell and Butler (1938) and Spies et al. (1938). Because of the mild and transient nature of the flushing effect, the IOM justified a UF of 1.5 to apply to the LOAEL, leading to determination of a UL of 35 mg per day for nictotinic acid. The IOM noted that 35 mg per day dose, however, may trigger the flushing reaction in a few persons. It is noteworthy that the clinical studies from which the IOM 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, thus increasing the likelihood of this undesirable effect. IOM (1998) also noted that the flushing effect was not associated with nicotinamide exposure but determined that the UL for nicotinic acid, if based on the flushing effect, would be protective against any potential adverse effects of nicotinamide. The IOM (1998) report did not evaluate an UL for IHN.

European Commission, Scientific Committee on Food (EC SCF 2002). In 2002, the EC SCF published its report on nicotinic acid and nicotinamide. The EC SCF (2002) reported that the more severe forms of toxicity (such as hepatotoxicity) of nicotinic acid occur only at doses greater than 500 mg per day but identified a LOAEL of 30 mg per day, based on occasional skin flushing in the same studies (i.e., Sebrell and Butler 1938; Spies et al. 1938) relied upon by the IOM. The EC SCF justified its identification of the vasodilatory (flushing) effects as the critical adverse effect (that is, as the *hazard* of concern in its UL risk assessment) based not only on the nuisance of discomfort but also on the hypothetical possibility of exaggeration of postural hypotension and a potentially related increased risk of falls, which are a common cause of morbidity and mortality in the elderly. No evidence was identified in the human clinical literature to support this supposition since the EC SCF review was published. An UF of 3 was applied to allow for a slight effect that was reported in a small number of subjects but taking into account the step dose-response relationship, resulting in an UL of 10 mg per day.

Since nicotinamide does not produce a flushing response, the EC SCF identified a NOAEL of 25 mg per kg bw per day based on the reporting of no significant adverse effects in trials investigating the possible benefits of nicotinamide in patients with or at risk of diabetes (Pozzilli et al. 1995). A UF of 2 was used to account for the slower elimination of nicotinamide in adults, considering the Pozzilli

et al. 1995 study had some subjects that were children. Therefore, a NOAEL value of 12.5 mg per kg bw per day was used to establish an UL of 900 mg per day for nicotinamide in a 72-kg adult. The EC SCF (2002) report did not evaluate an UL for IHN.

European Food Safety Authority (EFSA 2009). The EFSA (2009) performed an evaluation for IHN as a source of niacin added for nutritional purposes in food supplements. Based on its evaluation, the EFSA Panel determined that nicotinate from inositol hexanicotinate is bioavailable and a source of niacin. The Panel used the already established nicotinic acid UL of 10 mg per day from the EC SCF (2002) evaluation to derive the UL for IHN. The panel noted that, given the nicotinic acid was based on a NOAEL value identified from flushing effects, the UL would be conservative for IHN since nicotinic acid is slowly released from IHN and the flushing effect is not likely to occur when it is used as a source of niacin. However, at the time of this review, there was a lack of studies adequately supporting the absence of a flushing effect. The Panel noted that a daily dose of 10 mg nicotinic acid given as IHN would amount to a daily dose of 11 mg IHN, and that this dose when used for food supplement purposes would be of no safety concern.

European Food Safety Authority (EFSA 2019). The EFSA (2019) assessment evaluated nicotinamide riboside chloride (NR chloride) as a novel food, which included an evaluation on its safety as a food supplement at proposed use levels of 300 mg per day as a source of niacin. As part of the evaluation, the EFSA Panel concluded that NR is a source from which nicotinamide is bioavailable. The Panel derived a NOAEL value of 300 mg per kg bw per day for NR chloride from two unpublished repeat dose toxicity studies in rats and dogs (Thorsrud 2018; Bhoite et al. 2015), noting that the same effects observed at 1,000 and 3,000 mg per kg bw per day (e.g., changes in some hematology parameters and histopathology in various organs) observed in rats were reported in studies with nicotinamide administered at 1,260 mg per kg bw per day (equimolar to 3,000 mg per kg bw per day of NR chloride). No adverse effects were reported in an unpublished, one generation reproductive toxicity study in rats; the EFSA Panel identified the highest dose level in this study as the NOAEL value from this study (equivalent to 675 mg per kg bw per day in males and 1,088 mg per kg bw per day in females) (Ganiger 2016). In addition, an unpublished developmental toxicity study in rats was reviewed,

from which the EFSA Panel identified a NOAEL value of 325 mg per kg bw per day for maternal and embryo/fetotoxicity for NR chloride (Geetha Rao 2016). However, the Panel noted that the embryo/fetotoxicity findings starting at 750 mg per kg bw per day were considered secondary to maternal toxicity.

Human clinical studies considered by EFSA (2019) reported no safety concerns following intervention with NR chloride at doses of 100 mg for 1 day up to 2,000 mg per day up to 12 weeks at the time of the evaluation (Airhart et al. 2017; Dollerup et al. 2018; Martens et al. 2018; Conze et al. 2019). However, the NOAEL value of 300 mg per kg bw per day from the 90-day study in rats was carried forward as the basis of the Panel's risk calculations for NR chloride as a novel food. Using this NOAEL value, the Panel calculated a margin of exposure (MOE) of 70 for the proposed maximum use level of 300 mg per day for NR chloride (i.e., 4.3 mg per kg bw per day in a 70-kg adult). The Panel noted that, in light of the available human data on NR, the MOE was considered sufficient for adults excluding pregnant and lactating women. A separate MOE of 76 was calculated based on the NOAEL of 325 mg per kg bw per day from the developmental toxicity animal study (Geetha Rao 2016). Due to a lack of available data to justify accepting a lower MOE value than 100, the Panel concluded intake of up to 230 mg NR chloride per day for pregnant and lactating women as acceptable.

A tolerable upper intake limit for this compound has not been assessed by the EFSA. The EFSA (2019) Panel's charge was to specifically evaluate the safety of NR as a novel food at the proposed use level of 300 mg per day. The Panel relied heavily on rodent toxicology data with support from the limited human clinical studies available at the time of review. Since this EFSA assessment, an additional eleven human clinical trials with NR intervention levels up to 1,000 mg per day (Ahmadi et al. 2023; Bhandari et al. 2025; Brakedai et al. 2022; Elhassan et al. 2019; McDermott et al. 2024; Remie et al. 2020; Presterud et al. 2024; Wang et al. 2022; Vreones et al. 2023; Lapatto et al. 2023; Wu et al. 2025) and one study at 3,000 mg per day (Berven et al. 2023) have become available, none of which identified serious adverse effects related to NR. In addition, a more recent repeat dose oral toxicity study conducted with a synthetic NR chloride identified NOAEL values of 500 and 1,200 mg per kg bw per day for male and female rats, respectively (Marinescu et al. 2020), higher than the NOAEL value of 300 mg per kg bw per day used by the 2019 EFSA Panel.

Expert Group on Vitamins and Minerals (EVM 2003). The EVM's 2003 report concluded that, for both nicotinic acid and nicotinamide, "there are insufficient data from human or animal studies to establish a safe upper level..." Nevertheless, the EVM developed a guidance level for supplementation based solely on the flushing effect consistently reported at intakes of 50 mg per day (Sebrell and Butler 1938; Spies et al. 1938). An UF of 3 was applied to yield an UL of 17 mg per day for supplemental nicotinic acid (not applicable to extended-release preparations).

Like the EC SCF, the EVM established a safe level for nicotinamide distinct from that for nicotinic acid. The EVM identified no adverse effects for nicotinamide at intakes of 25 mg per kg bw per day (Pozzilli et al. 1995) and 42 mg per kg bw per day (Lampeter et al., 1998) but used an UF of 3 for interindividual variability since the study population was specific to Type 1 diabetics to establish an 8.3 mg per kg bw per day guidance value. The derived guidance level for a 60-kg person was 500 mg per day of supplemental nicotinamide per day. Assuming an intake of not more than 57 mg per day from foods, the EVM identified 560 mg per day as the guidance level for total intake of nicotinamide from all sources. The EVM did not establish a guidance level for IHN.

Chinese Nutrition Society (CNS 2023). The CNS derived an UL value of 35 mg per day for niacin (niacin equivalents) in adults. In addition, the CNS derived UL values of 290-310 mg per day in adults for nicotinamide, depending on age and pregnancy status.

Food Safety and Standards Authority of India (FSSAI 2018). The FSSAI determined the UL for niacin in adults to be 35 mg per day, based on a review of available literature and citing IOM (1998).

Republic of Korea (ROK 2020). The ROK Ministry of Health and Welfare published its general approach to evaluating data for setting DRI values. Based on this approach, UL values of 35 and 30 mg per day were derived for niacin (niacin equivalent) in adults ages ³19 and 18 years, respectively. In addition, UL values of 1,000 and 800 mg per day were derived for nicotinamide in adults ages ³19 and 18 years, respectively.

CRN Recommendations

The goal of the current update to CRN's supplemental UL for niacin was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that warrant a change to CRN's supplemental ULs for the niacin forms previously developed for adults. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized. As discussed above, other methodologies have been used by some government agencies that have relied on human clinical or animal toxicology data to derive associated UL values.

CRN's safety methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The table below summarizes the key human clinical studies considered in deriving updated UL values for supplemental intakes by CRN according to its principal points of departure for risk assessment (as described in the Methods). As described in the Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0).

Approximately 25 human clinical trials published since the 3rd edition of the book (i.e., starting in 2014) were identified that met the inclusion criteria for the current update.[5] A full literature review is outside the scope of this chapter; therefore, only studies identified in the updated search that are most pertinent[6] to deriving a revised UL for nicotinic acid, nicotinamide, NR, or IHN based on CRN's methodology, are summarized below together with key studies already summarized in the 3rd edition.

[5] Given the relatively small number of studies identified for NR (as a newer form of vitamin B3), CRN's inclusion criteria were modified for this chapter to include all studies that administered NR orally in adults for a minimum of one week.
[6] Where numerous relevant studies were identified, those most pertinent to the UL derivation are included in the table as representative studies. Prioritization was given to studies at dose levels informing the UL and studies with higher weighting based on CRN's Methods (e.g., duration, number of participants, randomization, etc.).

Key Studies Considered for the CRN UL for Niacin Forms in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)	Duration	NOAEL (mg/day)	LOAEL (mg/day)
Nicotinic Acid Immediate Release (based on gastrointestinal effects)[a]							
McKenney et al. 1994	Double blind trial	Healthy volunteers[b]	46	0, 500, 1,000, 1,500, 2,000, 3,000	6 weeks	500	1,000
Javadian et al. 2024	Randomized controlled trial	Patients on maintenance hemodiaslysis	98	0, 600	8 weeks	600	N/A
Nicotinic Acid Extended-Release (based on liver enzyme effects)[c]							
McKenney et al. 1994	Double blind trial	Volunteers with low-density lipoprotein cholesterol levels greater than 4.14 mmol/L	46	0, 500, 1,000, 1,500, 2,000, 3,000	6 weeks	500	1,000
Figueiredo et al. 2014	Randomized, controlled crossover trial	Healthy volunteers[d]	18	1,000	7 days	1,000	N/A
Nicotinamide (based on liver enzyme effects)[c]							
Pozzilli et al. 1995	Double blind trial	Patients with insulin-dependent diabetes mellitus	56	0, 1,500	12 months	1,500	N/A
Hui et al. 2020	Randomized, double blind trial	Patients with glaucoma	57	0, 1,500 + 3,000	6 weeks + 6 weeks	1,500-3,000	N/A
El Ters et al. 2020	Randomized, double blind trial	Patients with autosomal dominant polycystic kidney disease	36	0, 1,800	12 months	1,800	N/A
Libri et al. 2014	Exploratory dose escalation trial	Patients with Friedreich's ataxia	10	3,000 – 8,000	8 weeks	N/A	3,000 (liver toxicity effects)
Nicotinamide Riboside (NR)[c]							
Lapatto et al. 2023	Non-randomized, open label trial	Twin pairs (20)	40	0, 1,000	4 months[f]	1,000	N/A
Wu et al. 2025	Randomized, double blind, placebo-controlled, crossover trial	Adults with subjective cognitive impairment (>55 years of age)	46	0, 1,000	8 weeks	1,000	N/A

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)	Duration	NOAEL (mg/day)	LOAEL (mg/day)
Conze et al. 2019	Randomized, double blind, placebo-controlled, parallel trial	Healthy volunteers	140	0, 100, 300, 1,000	8 weeks	1,000	N/A
McDermott et al. 2024	Randomized, double blind, parallel trial	Patients with peripheral artery disease	90	0, 1,000[e]	6 months[f]	1,000	N/A
Dollerup et al. 2018	Randomized, double blind, placebo-controlled clinical trial	Healthy, obese Caucasian men	40	0, 2,000	12 weeks	2,000	N/A
Wang et al. 2022	Randomized, double-blind, placebo-controlled trial	Heart failure patients with reduced ejection fraction	30	0, 2,000	9 weeks[f]	2,000	N/A
Berven et al. 2023	Randomized, double blind, placebo-controlled trial	Patients with Parkinson's disease	20	0, 3,000	4 weeks	3,000	N/A
Inositol Hexanicotinate (IHN) Formulations[c]							
Sunderland et al. 1988	Double blind trial	Patients with Raynaud's disease	23	0, 4,000	3 months	4,000	N/A

N/A, not applicable
[a] flushing label warning needed (based on threshold >35 mg/day)
[b] with low-density lipoprotein cholesterol levels greater than 4.14 mmol/L
[c] flushing warning label not needed
[d] with plasma HDL-C levels < 40 mg/dL
[e] also included a third group receiving 1,000 mg NR + 125 mg resveratrol per day
[f] duration at full dose; does not reflect additional exposure to lower doses during titration phase

Nicotinic Acid

With its transient and nonpathological effects, the flushing reaction in response to supplemental nicotinic acid is characterized as a *nuisance* effect and not as a *true hazard* (as described in CRN's methodology). When high intakes result from supplementation, appropriate product labeling can alert the consumer of the potential flushing effect. Thus, flushing does not qualify as a hazard for supplemental intakes of nicotinic acid. Nevertheless, an UL for flushing based on available human clinical data was previously derived by CRN based on a threshold value of 35 mg per day for adults for both immediate and extended-release forms of nicotinic acid.

The CRN UL for adults for excessive supplemental nicotinic acid is based on the hepatotoxic effects (e.g., increases in serum transaminase enzymes of liver origin) at much higher doses determined to reflect *true hazard*. Considering the infrequent occurrence at the LOAEL levels of intake and the reversible nature of mild, short-term hepatotoxicity, the NOAEL values are identified as the CRN UL values for supplements, provided that formulations carry appropriate labeling for potential flushing effects.

While there are only two anecdotal cases of reported hepatotoxic effects at intakes less than 1,000 mg per day, many uncertainties exist in these cases regarding the amount consumed as well as the presence or absence of pre-existing or confounding conditions such as alcoholism or other compromises of liver function. Therefore, these studies were not relied on in setting the UL. However, the clinical trial data reported from 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 both immediate release and extended-release forms of nicotinic acid based on gastrointestinal effects or liver toxicity effects, respectively. Therefore, 500 mg per day is identified as the NOAEL for immediate release nicotinic acid following the CRN process. Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 500 mg per day for adults. This UL value is unchanged from the 3rd edition.

It should be noted, however, that the adverse reactions to 1,000 mg per day of immediate-release nicotinic acid were mainly gastrointestinal effects, which generally have less potential for serious outcomes, rather than the liver toxicity that results in some persons consuming 1,000 mg per day of extended-release nicotinic acid. With proper labeling, consumers can be aware of gastrointestinal effects and correct as needed. These differences warrant advising a more conservative UL for extended-release nicotinic acid than for the immediate-release form. Therefore, a two-fold UF was applied in the 3rd edition to derive CRN's UL for supplemental intake in adults for extended-release nicotinic acid, based on the clinical trial results from McKenney et al. 1994. New studies identified since the 3rd edition support the previously derived CRN supplemental UL. Therefore, 500 mg per day is identified as the NOAEL for extended-release nicotinic acid following the CRN process. An UF of 2 is applied to yield an UL of 250 mg per day for adults.

It should be noted that the reports by the IOM, the EC SCF, and the EVM did not set NOAEL or LOAEL values based on the hepatotoxic effects of nicotinic acid and did not address extended-release nicotinic acid forms in any detail. In those reviews, hepatotoxic effects occurring with substantial frequency were identified following intakes of ~3,000 mg per day.

The lack of hepatotoxic effects reported in the clinical trial by Grundy et al. (2002) challenge the validity of the assumption that extended- release nicotinic acid is necessarily more toxic than immediate-release nicotinic acid if used in an appropriate manner, with a gradual escalation of the dose and careful clinical monitoring. Grundy et al. (2002) achieved the highest doses of extended-release nicotinic acid with weekly step-wise increases (e.g., 375 mg per day extended-release nicotinic acid at bedtime in week 1; 500 mg per day in week 2; 750 mg per day in week 3; and 1,000 mg per day in week 4). These results indicate that 1,000 mg per day of extended-release nicotinic acid can be safely consumed with a step-wise escalation of intake and medical supervision.

Nicotinamide

The clinical trials used to derive the previous CRN UL for nicotinamide were determined to support a NOAEL of 25 mg per kg bw per day. For example, Pozzilli et al. (1995) reported no significant difference in adverse effects between control and treated groups in patients with insulin dependent diabetes mellitus. Because some of these trials were performed with subjects younger than 18 years old who had lower than fully adult body weights, 60 kg was used to calculate a NOAEL value 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. However, other studies have reported adverse liver effects of nicotinamide intakes of more than 3,000 mg per day (Rader et al. 1992). While several studies published since the derivation of the previous CRN UL that do not report adverse effects in patients in doses up to 1,500 – 3,000 mg per day, these studies did not specifically assess liver enzymes or other liver-related parameters (Hui et al. 2020; El Ters et al. 2020). As such, these newer studies do not adequately assess potential liver effects and are not considered to be sufficient justification for deriving a higher UL value for nicotinamide. Therefore, 1,500 mg per day is identified as the

NOAEL for nicotinamide following the CRN process. Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 1,500 mg per day for adults. This UL is unchanged from the 3rd edition.

Nicotinamide Riboside (NR)

NR was not assessed in the 3rd edition. None of the fifteen human clinical trials identified with NR (as NR chloride) reported any serious adverse effects. Twelve of these studies administered NR up to 1,000 mg per day (Airhart et al. 2017; Ahmadi et al. 2023; Bhandari et al. 2025; Brakedal et al. 2022; Conze et al. 2019; Elhassan et al. 2019; Martens et al. 2018; McDermott et al. 2024; Remie et al. 2020; Vreones et al. 2023; Lapatto et al. 2023; Wu et al. 2025). Additional studies included NR intervention levels up to 3,000 mg per day (Dollerup et al. 2018; Wang et al. 2022; Berven et al. 2023). Despite the lack of any serious adverse effects across these studies, given the wide variability in dose and individual considerations regarding study design, a modified approach based on CRN's methodology was implemented in which the available clinical evidence was considered together for the purposes of deriving an UL value for NR.

- One randomized, double blind, placebo-controlled clinical trial study administered NR at 2,000 mg per day for twelve weeks, resulting in a mean dose of 19.08 mg per kg bw per day for the obese male study population (Dollerup et al. 2018). However, this same dose would equate to only 28.57 mg per kg per day in a 70-kg adult.
- One randomized, double blind, placebo-controlled clinical trial study administered NR at 2,000 mg per day for nine weeks after titration (total exposure twelve weeks) (Wang et al. 2022). While this study was relatively small in size and short in duration, it included *a priori* laboratory parameters relevant to safety. In addition, the concomitant medication use during the study is not expected to have affected the safety profile of NR.
- One randomized, double blind, placebo-controlled clinical trial study administered NR at 3,000 mg per day for four weeks (Berven et al. 2023). While the size of this study (n=20) limits its utility to serve as the basis of the UL, it provides additional support for the derived UL value.

Based on the multiple lines of evidence identified in the available clinical dataset, the NOAEL value

of 2,000 mg per day (as NR chloride) from Wang et al. (2022) is identified as the NOAEL for NR following the modified CRN process. Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 2,000 mg per day for adults. This UL value is further supported by the CRN UL value for nicotinamide. Since NR is partially metabolized to nicotinamide and 1 mg of NR chloride equates to 0.42 mg of nicotinamide as previously discussed, an UL value of 2,000 mg NR per day would equate to 840 mg per day of nicotinamide. This dose is well below the 1,500 mg per day UL CRN derived for nicotinamide based on liver enzyme effects. In addition, since nicotinamide is not associated with flushing effects, the threshold level for a flushing warning is not relevant for NR.

Inositol Hexanicotinate (IHN)

Clinical trials using IHN range from 600 to 4,000 mg intervention daily. No adverse effects have been identified in clinical trials even when 4,000 mg per day IHN was administered orally to humans for 3 months (Sunderland et al. 1988). Clinical trials on IHN have not been specifically designed to assess safety of IHN; however, no meaningful adverse effects have been noted in several well-designed clinical trials. No relevant studies were identified for IHN in a recent search for publications since the 3rd edition. Based on the scope of the current update for this 4th edition, the previous CRN UL value is maintained. Consistent with CRN's methodology, an UF of 1 was applied to the NOAEL value of 4,000 mg per day (Sunderland et al., 1988) to yield an UL of 4,000 mg per day for adults, as described in the 3rd edition.

Quantitative Summary for Nicotinic Acid (Immediate and Extended-Release) in Adults

CRN (2024) UL, supplemental intake—immediate release	500 mg/day (with warning label for potential flushing effects)[a]
CRN (2024) UL, supplemental intake—based on flushing effect	35 mg/day
CRN (2024) UL, supplemental intake—extended-release niacin	250 mg/day (step-wise increases; with warning label for potential flushing effects)[a]
IOM (1998) UL, total intake	35 mg/day
EC SCF (2002) UL, total intake	10 mg/day
EC supplement maximum	Not determined
EVM (2003), guidance level, supplemental intake	17 mg/day
CNS (2023) UL, total intake	35 mg/day
FSSAI (2018) UL, total intake	35 mg/day
ROK (2020), UL total intake	35 mg/day (30 mg/day for ages 15-18 years)

[a] Considering the infrequent occurrence at the LOAEL levels of intake and the reversible nature of mild, short-term hepatotoxicity, the NOAEL values are identified as the CRN UL values for supplements, provided that formulations carry appropriate labeling for potential flushing effects (i.e., >35 mg/day).

Quantitative Summary for Nicotinamide in Adults

CRN UL (2024), supplemental intake	1,500 mg/day
IOM UL (1998), total intake	35 mg/day
EC SCF (2002) UL, total intake	900 mg/day
EC supplement maximum	Not determined
EVM (2003), guidance level, supplemental intake	500 mg/day
CNS (2023) UL, total intake	290-310 mg/day
FSSAI (2018) UL, total intake	Not determined
ROK (2020), UL total intake	1,000 mg/day (800 mg/day for ages 15-18 years)

Quantitative Summary for Nicotinamide Riboside (NR) in Adults

CRN UL (2024), supplemental intake	2,000 mg/day
IOM (1998) UL, total intake	Not determined
EFSA (2019), safe level	300 mg/day (230 mg/day in pregnant and lactating women)[a]
EC supplement maximum	Not determined
EVM (2003), guidance level, supplemental intake	Not determined
CNS (2023) UL, total intake	Not determined
FSSAI (2018) UL, total intake	Not determined
ROK (2020), UL total intake	Not determined

[a] EFSA (2019) did not derive an UL value for NR.

Quantitative Summary for Inositol Hexanicotinate in Adults

CRN UL (2024), supplemental intake	4,000 mg/day
IOM (1998) UL, total intake	Not determined
EFSA (2009) UL, supplemental intake	11 mg/day
EC supplement maximum	Not determined
EVM (2003), guidance level, supplemental intake	Not determined
CNS (2023) UL, total intake	Not determined
FSSAI (2018) UL, total intake	Not determined
ROK (2020), UL total intake	Not determined

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