SUMMARY

Niacin functions as a cosubstrate or coenzyme for the transfer of the hydride ion with numerous dehydrogenases. The primary criterion used to estimate the Recommended Dietary Allowance (RDA) for niacin is the urinary excretion of niacin metabolites. No adjustment is made for bioavailability, but the requirement is expressed in niacin equivalents (NEs), allowing for some conversion of the amino acid tryptophan to niacin. The RDA for adults is 16 mg/day of NEs for men and 14 mg/day of NEs for women. Recently, the median intake of preformed niacin from food in the United States was approximately 28 mg for men and 18 mg for women, and the ninety-fifth percentile of intake from both food and supplements was 40 to 70 mg of NEs, depending on age. In two Canadian populations the median intake of preformed niacin was approximately 41 mg/day for men and 28 mg/day for women. The Tolerable Upper Intake Level (UL) for niacin for adults is 35 mg/day, which was based on flushing as the critical adverse effect.

BACKGROUND INFORMATION

The term niacin refers to nicotinamide (nicotinic acid amide), nicotinic acid (pyridine-3-carboxylic acid), and derivatives that exhibit the biological activity of nicotinamide. The nicotinamide moiety of the pyridine nucleotide coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phos-
phate (NADP) acts as a hydride ion acceptor or donor in many biological redox reactions. NAD has also been shown to be required for important nonredox adenosine diphosphate (ADP)–ribose transfer reactions involved in deoxyribonucleic acid (DNA) repair and calcium mobilization (Kim et al., 1994; Lautier et al., 1993; Lee et al., 1989). The amino acid tryptophan is converted in part to nicotinamide and thus can contribute to meeting the requirement for niacin.

Function

In the form of the coenzymes NAD and NADP, niacin functions in many biological redox reactions. NAD functions in intracellular respiration and as a codehydrogenase with enzymes involved in the oxidation of fuel molecules such as glyceraldehyde 3-phosphate, lactate, alcohol, 3-hydroxybutyrate, pyruvate, and α-ketoglutarate. NADP functions in reductive biosyntheses such as in fatty acid and steroid syntheses and, like NAD, as a codehydrogenase—as in the oxidation of glucose 6-phosphate to ribose 5-phosphate in the pentose phosphate pathway.

Three classes of enzymes cleave the β-N-glycosylc bond of NAD to free nicotinamide and catalyze the transfer of ADP-ribose in nonredox reactions (Lautier et al., 1993). Two of the three classes catalyze ADP-ribose transfer to proteins: mono-ADP-ribosyltransferases and poly-ADP-ribose polymerase (PARP). The third class promotes the formation of cyclic ADP-ribose, which mobilizes calcium from intracellular stores in many types of cells (Kim et al., 1994).

The enzyme PARP is found in the nuclei of eukaryotic cells and catalyzes the transfer of many ADP-ribose units from NAD to an acceptor protein and also to the enzyme itself. These nuclear poly-ADP-ribose proteins seem to function in DNA replication and repair and in cell differentiation. DNA damage greatly enhances the activity of PARP (Stierum et al., 1994); PARP activity is strongly correlated with cellular apoptosis (Stierum et al., 1994).

Physiology of Absorption, Metabolism, and Excretion

Absorption and Transport

Absorption of nicotinic acid and nicotinamide from the stomach and the intestine is rapid (Bechgaard and Jespersen, 1977) and at low concentrations is mediated by sodium ion-dependent facilitated diffusion. At higher concentrations, passive diffusion predominates,
NIACIN 125

with doses of 3 to 4 g of niacin almost completely absorbed (Bechgaard and Jespersen, 1977). Glycohydrolases in the liver and intestines catalyze the release of nicotinamide from NAD (Henderson and Gross, 1979). Nicotinamide is then transported to tissues to be used in synthesis of NAD when needed. Both forms of the vitamin enter cells by simple diffusion; however, both nicotinic acid and nicotinamide also enter erythrocytes by facilitated transport (Lan and Henderson, 1968).

Metabolism and Excretion

The niacin coenzymes NAD and NADP are synthesized in all tissues of the body from nicotinic acid or nicotinamide. Tissue concentrations of NAD appear to be regulated by the concentration of extracellular nicotinamide, which in turn is under hepatic control and is hormonally influenced. Hydrolysis of hepatic NAD allows the release of nicotinamide for transport to tissues that lack the ability to synthesize the NAD and NADP coenzymes from tryptophan. In the liver some excess plasma nicotinamide is converted to storage NAD (i.e., NAD not bound to enzymes). Tryptophan and nicotinic acid also contribute to storage NAD following the biosynthetic pathway, going through NAMN, which is then reamidated to NAD. In the degradation of NAD, the nicotinamide formed can be reconverted to NAD via nicotinamide ribonucleotide. Nicotinamide can be deamidated in the intestinal tract by intestinal microflora (Bernofsky, 1980).

The body’s niacin requirement is met not only by nicotinic acid and nicotinamide present in the diet, but also by conversion from the dietary protein containing tryptophan. The relative contribution of tryptophan is estimated as follows: 60 mg of tryptophan = 1 mg of niacin = 1 mg of niacin equivalents (Horwitt et al., 1981).

Excess niacin is methylated in the liver to $N^1$-methyl-nicotinamide, which is excreted in the urine along with the 2- and 4-pyridone oxidation products of $N^1$-methyl-nicotinamide. The two major excretion products are $N^1$-methyl-nicotinamide and its pyridone derivative (Mrochek et al., 1976). The proportions differ somewhat depending on the amount and form of niacin ingested and the niacin status of the individual.

Clinical Effects of Inadequate Intake

Pellagra is the classic manifestation of a severe niacin deficiency. It is characterized by a pigmented rash that develops symmetrically
in areas exposed to sunlight; changes in the digestive tract that are associated with vomiting, constipation or diarrhea, and a bright red tongue; and neurological symptoms including depression, apathy, headache, fatigue, and loss of memory. Pellagra was common in the United States and parts of Europe in the early twentieth century in areas in which corn or maize (which is low in both niacin and the amino acid tryptophan) was the dietary staple. Although a world-wide problem, pellagra has virtually disappeared from industrialized countries except for its occurrence in chronic alcoholism and in individuals with conditions that disrupt tryptophan pathways. It still appears in India and parts of China and Africa. For example, pellagra was reported in Mozambican refugees in Malawi (Malfait et al., 1993).

SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR NIACIN

Niacin status and dietary requirement can be estimated by using biochemical or clinical endpoints of niacin deficiency. Biochemical changes occur well before the appearance of overt signs of deficiency. Biochemical markers include daily urinary excretion of methylated metabolites, the ratio of 2-pyridone to $N^1$-methyl-nicotinamide in urine, erythrocyte pyridine nucleotides, oral dose uptake tests, erythrocyte nicotinamide adenine dinucleotide (NAD), and plasma 2-pyridone derivative.

*Urinary Excretion*

The most reliable and sensitive measures of niacin status are urinary excretion of the two major methylated metabolites, $N^1$-methyl-nicotinamide and its 2-pyridone derivative ($N^1$-methyl-2-pyridone-5-carboxamide). Criteria for interpreting urinary $N^1$-methyl-nicotinamide excretion amounts in adults and pregnant women indicate that for adults, 24-hour excretion rates of less than 5.8 $\mu$mol/day represent deficient niacin status and 5.8 to 17.5 $\mu$mol/day represents low status (Sauberlich et al., 1974). The ratio of the 2-pyridone to $N^1$-methyl-nicotinamide, although independent of age and creatinine excretion, is a measure of protein adequacy rather than niacin status (Shibata and Matsuo, 1989). It is relatively insensitive to a marginal niacin intake of 10 mg/day of niacin equivalents (NEs) and has been shown to be not totally reliable for evaluating an intake of 6 mg/day of NEs (Jacob et al., 1989). The ratio of the 6-pyridone ($N^1$-methyl-nicotinamide-3-carboxamide) to $N^1$-methyl-
nicotinamide appears to be associated with the development of clinical symptoms of pellagra, principally dermatitis (Dillon et al., 1992).

Plasma Concentrations

In plasma the 2-pyridone derivative drops below detection limits after a low niacin intake (Jacob et al., 1989). With an oral niacin load (nicotinamide at 20 mg/70 kg body weight), postdose changes in 2-pyridone in both plasma and urine were more responsive to niacin status than changes seen in $N^1$-methyl-nicotinamide. Plasma concentrations of other niacin metabolites and of niacin are not useful markers of niacin status.

Erythrocyte Pyridine Nucleotides

Analysis of erythrocyte NAD concentration promises to be a sensitive indicator of niacin depletion. In an experimental study in which adult male subjects were fed low-niacin diets containing either 6 or 10 mg NE/day, the erythrocyte NAD concentration decreased by 70 percent, whereas the NADP concentration remained unchanged (Fu et al., 1989). An earlier study reported a similar decrease in NAD relative to NADP in fibroblasts grown in niacin-restricted culture (Jacobson et al., 1979). Erythrocyte NAD concentrations provided a marker of niacin depletion equally as sensitive and reliable as excretion of urine metabolites in a study of seven healthy young men (Fu et al., 1989) and in an experimental niacin depletion study of elderly subjects (Ribaya-Mercado et al., 1997).

Transfer of Adenosine Diphosphate Ribose

A possible functional measure for niacin status could be polyadenosine diphosphate (ADP) ribosylation, because ADP ribosylation may contribute to gene stability (poly-ADP-ribose polymerase in the nucleus) and may function in deoxyribonucleic acid (DNA) replication and repair (Stierum et al., 1994). However, the assays have not been developed or refined well enough to be used to judge niacin status at present.

Pellagra

Clinical pellagra may represent various degrees of combined niacin and riboflavin deficiencies (Carpenter and Lewin, 1985).
Deficiencies of other micronutrients (e.g., pyridoxine and iron) required to convert tryptophan to niacin may also contribute to the appearance of pellagra. Because pellagra is a late and serious manifestation of deficiency, it was determined that the average requirement must exceed the amount required to prevent pellagra.

FACTORS AFFECTING THE NIACIN REQUIREMENT

Bioavailability

Niacin in mature cereal grains is largely bound and thus is only about 30 percent available; alkali treatment of the grain increases the percentage absorbed (Carpenter and Lewin, 1985; Carter and Carpenter, 1982). Niacin in the coenzyme nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NAD/NADP) form in meats appears to be much more available. Niacin added during enrichment or fortification is in the free form and thus highly available. Foods that contain niacin in the free form include beans and liver. Quantitative data are not available on which to base adjustments for the bioavailability from different types of foods.

The conversion efficiency of tryptophan to niacin, although assumed to be 60:1 (Horwitt et al., 1981), varies depending on a number of dietary and metabolic factors. The requirement for preformed niacin is increased by factors that reduce the conversion of tryptophan to niacin (McCormick, 1988), including low tryptophan intake; carcinoid syndrome in which tryptophan is preferentially oxidized to 5-hydroxytryptophan and serotonin; prolonged treatment with the drug Isoniazid, which competes with pyridoxal 5'-phosphate, a vitamin B₆-derived coenzyme required in the tryptophan-to-niacin pathway; and Hartnup’s disease, an autosomal recessive disorder that interferes with the absorption of tryptophan in the intestine and kidney.

The efficiency of the conversion of dietary tryptophan to niacin is decreased by deficiencies of other nutrients (see “Nutrient-Nutrient Interactions”). Conversion efficiency may increase with some dietary restrictions because of changes in activities of pathway enzymes including tryptophan oxygenase, quinolinate phosphoribosyltransferase, and picolinate carboxylase.

The requirement for preformed niacin as a proportion of the total niacin requirement tends to be lower with higher tryptophan intakes (a greater proportion of tryptophan is available for conversion to NAD once protein synthesis needs are met) and pregnancy.
(the conversion of tryptophan to niacin is more efficient [Knox, 1951; Rose and Braidman, 1971; Wertz et al., 1958]). Oral contraceptives that contained high doses of estrogen have also been found to increase conversion efficiency (Rose and Braidman, 1971; Wertz et al., 1958). The priority for body tryptophan utilization is protein synthesis before NAD or NADP synthesis.

The 60 to 1 conversion value represents the mean of a wide range of individual values found in human studies that measured the conversion of tryptophan to urinary niacin metabolites (Horwitt et al., 1981). Irrespective of dietary factors, substantial individual differences (30 percent) in the conversion efficiency of tryptophan to niacin have been reported (Horwitt et al., 1981; Patterson et al., 1980).

**Nutrient-Nutrient Interactions**

Interactions occur between riboflavin and vitamin B6 metabolism in which flavin mononucleotide (FMN) is required for the oxidase that forms coenzymic pyridoxal 5'-phosphate required for conversion of tryptophan to niacin (McCormick, 1989). There is also interdependence of enzymes within the tryptophan-to-niacin pathway where pyridoxal 5'-phosphate, flavin-adenine dinucleotide (FAD), and iron are functional. Hence, inadequate iron, riboflavin, or vitamin B6 status decreases the conversion of tryptophan to niacin. Data are not available to quantitatively assess the effects of these nutrient-nutrient interactions on the niacin requirement.

**Energy Intake and Expenditure**

No directly relevant studies were found that examined the effect of energy intake or expenditure on the niacin requirement. Examination of individual data from four studies showed no relationship between excretion of N1-methyl-nicotinamide and either energy intake or body weight (Goldsmith et al., 1952, 1956; Horwitt et al., 1956; Jacob et al., 1989). Studies of niacin requirements are consistently presented in relation to energy intake on the basis of the known biochemical function of niacin, as have been past recommendations for niacin intake (NRC, 1989).*

*It is recognized that studies of individuals in forced starvation situations have reported that individuals with the greatest initial body weights (and thus the greatest energy expenditure) developed signs of deficiency more rapidly than did others consuming similar diets but who weighed less initially. However, the panel could not quantify this difference as assessed by changes in available indicators of adequacy by those consuming typical diets in Canada and the United States.
Despite the lack of experimental data, the known biochemical function of niacin in the oxidation of fuel molecules suggests at least a small (10 percent) adjustment to reflect differences in the average energy utilization and size of men and women, a 10 percent increase in the requirement to cover increased energy use during pregnancy, and a small increase in the requirement to account for the efficiency of niacin use in milk production during lactation.

**FINDINGS BY LIFE STAGE AND GENDER GROUP**

*Infants Ages 0 through 12 Months*

*Method Used to Set the Adequate Intake*

As for other nutrients, the Adequate Intake (AI) level for niacin is set for infants based on the observed mean intake of infants fed principally with human milk.

*Ages 0 through 6 Months.* One study (Ford et al., 1983) of unsupplemented mothers estimated the niacin concentration of their milk at 1.8 mg/L. The adequate intake for niacin for infants ages 0 through 6 months is based on the reported mean volume of milk consumed by this age group (0.78 L/day; see Chapter 2) and the estimate of the niacin concentration in human milk of 1.8 mg/L (0.78 L × 1.8 mg/L = 1.4 mg). The tryptophan content of human milk is approximately 210 mg/L (Committee on Nutrition, 1985). Because of the high rate of protein turnover and net positive nitrogen retention in infancy, it is likely that the standard method for estimating niacin equivalents (NEs) would overestimate the contribution from tryptophan. Thus, the AI for niacin for infants is given in milligrams of preformed niacin only—2 mg/day after rounding up.

*Ages 7 through 12 Months.* No difference in human milk composition was noted between the first and second 6 months of lactation (Ford et al., 1983). If the reference body weight ratio method described in Chapter 2 to extrapolate from the AI for niacin for infants ages 0 through 6 months is used, the AI for preformed niacin for the older infants is 2 mg/day after rounding. The second method (see Chapter 2), extrapolating from the Estimated Average Requirement (EAR) for adults and adjusting for the expected variance to estimate a recommended intake, gives an AI of 4.1 mg of NEs. A 15 percent coefficient of variation (CV) is used (for discussion, see “Niacin EAR and RDA Summary, Ages 19 Years and Older”). This AI value
Niacin is expected to be higher than that obtained with the first method because it reflects NEs rather than preformed niacin.

Alternatively, the AI for niacin for infants ages 7 through 12 months can be calculated by using the estimated niacin content of 0.6 L of human milk and the average volume consumed by this age group (niacin content equals 1.1 mg), and adding the amount of niacin provided by solid foods (8 mg), as estimated by Montalto et al. (1985) (see Chapter 2). The result in NEs equals more than 9 mg/day. This value was judged to be unreasonably high because it is more than twice the extrapolated values and because mean intakes of older age groups appear to be much higher than their requirements. Thus the AI for niacin given in NEs is 4 mg/day for infants ages 7 through 12 months—the value extrapolated from estimates of adult requirements.

### Niacin AI Summary, Ages 0 through 12 Months

**AI for Infants**

- **0–6 months**: 2 mg/day of preformed niacin
  ≈ 0.2 mg/kg
- **7–12 months**: 4 mg/day of niacin equivalents
  ≈ 0.4 mg/kg

### Children and Adolescents Ages 1 through 18 Years

**Method Used to Estimate the Average Requirement**

No data were found on which to base the EAR for niacin for children or adolescents. In the absence of additional information, EARs and RDAs for children and adolescents have been estimated by using the method described in Chapter 2, which extrapolates from adult values.

### Niacin EAR and RDA Summary, Ages 1 through 18 years

**EAR for Children**

- **1–3 years**: 5 mg/day of niacin equivalents
- **4–8 years**: 6 mg/day of niacin equivalents

**EAR for Boys**

- **9–13 years**: 9 mg/day of niacin equivalents
- **14–18 years**: 12 mg/day of niacin equivalents

**EAR for Girls**

- **9–13 years**: 9 mg/day of niacin equivalents
- **14–18 years**: 11 mg/day of niacin equivalents

The RDA for niacin is set by using a coefficient of variation (CV)
of 15 percent (see Chapter 1 and the discussion of adult requirements that follows) because information is not available on the standard deviation of the requirement for these age groups; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for niacin the RDA is 130 percent of the EAR).

**RDA for Children**

- 1–3 years: 6 mg/day of niacin equivalents
- 4–8 years: 8 mg/day of niacin equivalents

**RDA for Boys**

- 9–13 years: 12 mg/day of niacin equivalents
- 14–18 years: 16 mg/day of niacin equivalents

**RDA for Girls**

- 9–13 years: 12 mg/day of niacin equivalents
- 14–18 years: 14 mg/day of niacin equivalents

**Adults Ages 19 Years and Older**

*Method Used to Estimate the Average Requirement*

The best biochemical measure for estimating the average requirement was judged to be niacin metabolite excretion data, namely the metabolites $N^1$-methyl-nicotinamide and its 2-pyridone derivative. These measures have been reported the most extensively. The niacin intakes that result in these measures being above the levels considered barely adequate represent some degree of body pool reserve. Niacin metabolites are not excreted until adequate tryptophan is available to meet needs for the synthesis of protein, nicotinamide adenine dinucleotide, and nicotinamide adenine dinucleotide phosphate (Fu et al., 1989; Vivian et al., 1958). Metabolite excretion measures are more sensitive to niacin depletion than are other biochemical measures, such as blood levels of pyridine nucleotides or tryptophan. Whereas pellagra is prevented with NEs of about 11 mg/day (at 2,500 kcal/day), restoration of niacin metabolite excretion beyond minimal occurs at intakes of NEs of about 12 to 16 mg/day. Excretion of $N^1$-methyl-nicotinamide rather than the 2-pyridone derivative is preferred as the target measure for estimating the niacin requirement because this metabolite better differentiates marginal from adequate niacin intakes (Jacob et al., 1989), interpretive guidelines exist for this metabolite (ICNND, 1963), and more data are available for this than for other metabolites.

An average niacin requirement can be estimated as the niacin intake corresponding to an excretion of $N^1$-methyl-nicotinamide
that is above the minimal excretion at which pellagra symptoms occur. Urinary excretion of $N^1$-methyl-nicotinamide was found to be 1.2 mg/day in men on low but adequate niacin diets that resulted in no signs or symptoms of pellagra (Horwitt et al., 1956; Jacob et al., 1989). Urinary $N^1$-methyl-nicotinamide excretion was found to be 0.6 mg/day in three females on corn-based, niacin-deficient diets that resulted in clinical signs and symptoms of pellagra (Goldsmith et al., 1952, 1955). A urinary excretion value for $N^1$-methyl-nicotinamide of 1.0 mg/day has been chosen as an interpolated level of niacin excretion; it reflects a niacin intake that is above the intake that results in clinical niacin deficiency and thus is minimal or barely adequate.

Niacin intakes (expressed in NEs) that would correspond to $N^1$-methyl-nicotinamide excretions of 1.0 mg/day are calculated from the results of four experimental studies in which NEs of 8 to 12 mg/day were fed (Table 6-1). A study by Patterson and colleagues (1980) was not used because no individual data were provided. In calculating the niacin intakes that would result in the $N^1$-methyl-nicotinamide excretion level of 1 mg/day, a linear relationship was assumed. This approach is conservative; if more niacin was fed, the ratio of niacin to the excretion of $N^1$-methyl-nicotinamide would become somewhat lower. Because all the studies were judged satisfactory in quality, a weighted average of the results was calculated. The overall average intake equivalent to the excretion of 1 mg/day of $N^1$-methyl-nicotinamide is 11.6 ± 3.94 (standard deviation), with a CV of 34 percent.

From Table 6-1, it might be interpreted that women require more niacin per 1,000 kcal than do men. However, the studies are too few and not sufficiently comparable to justify such a conclusion, especially considering a lack of evidence that utilization of niacin is less efficient for women than for men. The studies varied widely in methods, including the types of foods provided, which could have marked effects on the bioavailability of niacin. It is thus assumed that women have a slightly lower requirement than do men because of their size and average energy utilization. Therefore, the EAR is estimated to be 12 mg of NEs for men and 11 mg of NEs for women. Data are not available for determining whether the niacin requirement changes with age in adults.

The results of other studies were examined (Goldsmith, 1958; Goldsmith et al., 1956; Horwitt, 1958; Leklem et al., 1975), but coexisting deficiencies, a lack of valid dietary measurements, or both made it necessary to exclude them when deriving the EAR.
### TABLE 6-1 Experimental Human Studies of Niacin Intake and Urine N<sup>1</sup>-methylnicotinamide Excretion

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Regimen</th>
<th>NE Intake Calculated to Result in N&lt;sup&gt;1&lt;/sup&gt;-methylnicotinamide Excretion of 1.0 mg/d, Mean ± SD (CV%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldsmith et al., 1952</td>
<td>5 females, 25–54 y</td>
<td>Four fed a corn-based diet low in niacin and trp (7.7 mg of NEs) and one fed a wheat-based diet (9.5 mg of NEs) for up to 135 d. Supplemented with N&lt;sup&gt;1&lt;/sup&gt;-methylnicotinamide or trp.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.6 ± 3.0 (23%) or ≈6.8 mg of NEs/1,000 kcal</td>
</tr>
<tr>
<td>Goldsmith et al., 1955</td>
<td>3 females, 26–60 y</td>
<td>Fed wheat-based diet low in niacin and trp (8.3 mg of NEs) for up to 80 d. Supplemented with N&lt;sup&gt;1&lt;/sup&gt;-methylnicotinamide.</td>
<td>10.9 ± 0.9 (8%) or ≈5.8 mg of NEs/1,000 kcal</td>
</tr>
<tr>
<td>Horwitt et al., 1956</td>
<td>14 male mental patients, 30–65 y</td>
<td>Fed three ordinary food diets low in niacin and trp in a series of studies for up to 87 wk. Supplemented with N&lt;sup&gt;1&lt;/sup&gt;-methylnicotinamide or trp to provide 9–12 mg/d of NEs.</td>
<td>11.5 ± 4.5 (39%) or ≈4.9 mg of NEs/1,000 kcal</td>
</tr>
<tr>
<td>Jacob et al., 1989</td>
<td>7 males, 23–39 y</td>
<td>Gelatin-based diet of ordinary foods fed over 11 wk with varying ratios of trp and N&lt;sup&gt;1&lt;/sup&gt;-methylnicotinamide to provide 6 or 10 mg/d of NEs (and varying leucine).</td>
<td>11.3 ± 4.6 (41%) or ≈4.4 mg of NEs/1,000 kcal</td>
</tr>
<tr>
<td>Average of the four studies, two with females and two with males, on low-niacin diets (6–12 mg/d of NEs) for 4–24 wk</td>
<td></td>
<td></td>
<td>11.6 ± 3.9 (34%) or ≈4.8 mg of NEs/1,000 kcal</td>
</tr>
</tbody>
</table>

<sup>a</sup> NE = niacin equivalent (1 NE = 1 mg niacin = 60 mg tryptophan); SD = standard deviation; CV = coefficient of variation.

<sup>b</sup> trp = tryptophan.
Niacin EAR and RDA Summary, Ages 19 Years and Older

On the basis of the data in Table 6-1 and with a minor (approximately 10 percent) decrease for energy in women, the EAR is set at 12 mg/day of NEs for men and 11 mg/day of NEs for women.

**EAR for Men**

- 19–30 years: 12 mg/day of niacin equivalents
- 31–50 years: 12 mg/day of niacin equivalents
- 51–70 years: 12 mg/day of niacin equivalents
- > 70 years: 12 mg/day of niacin equivalents

**EAR for Women**

- 19–30 years: 11 mg/day of niacin equivalents
- 31–50 years: 11 mg/day of niacin equivalents
- 51–70 years: 11 mg/day of niacin equivalents
- > 70 years: 11 mg/day of niacin equivalents

The data in Table 6-1 also suggest a CV of the niacin requirement that is greater than 10 percent. The wide variation in the efficiency of converting tryptophan to niacin may contribute to the large apparent variation. Thus, a CV of 15 percent is used; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for niacin the RDA is 130 percent of the EAR).

**RDA for Men**

- 19–30 years: 16 mg/day of niacin equivalents
- 31–50 years: 16 mg/day of niacin equivalents
- 51–70 years: 16 mg/day of niacin equivalents
- > 70 years: 16 mg/day of niacin equivalents

**RDA for Women**

- 19–30 years: 14 mg/day of niacin equivalents
- 31–50 years: 14 mg/day of niacin equivalents
- 51–70 years: 14 mg/day of niacin equivalents
- > 70 years: 14 mg/day of niacin equivalents

**Pregnancy**

Method Used to Estimate the Average Requirement

There is no direct evidence that would suggest a change in the niacin requirement during pregnancy. To derive the EAR for pregnant women, it is estimated that the need for niacin increases by 3 mg/day of NEs to cover increased energy utilization and growth in
maternal and fetal compartments, especially during the second and third trimesters.

**Niacin EAR and RDA Summary, Pregnancy**

By adding 3 mg of NEs to the EAR of 11 mg of NEs for nonpregnant, nonlactating women, the EAR for pregnancy becomes 14 mg of NEs. No adjustment is made for the woman’s age.

**EAR for Pregnancy**

<table>
<thead>
<tr>
<th>Age</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>14 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>19–30 years</td>
<td>14 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>31–50 years</td>
<td>14 mg/day of niacin equivalents</td>
</tr>
</tbody>
</table>

The data in Table 6-1 suggest a CV for the niacin requirement that is greater than 10 percent. The wide variation in the efficiency of converting tryptophan to niacin may contribute to the larger apparent variation. Thus, a CV of 15 percent is used because information is not available on the standard deviation of the requirement for pregnant women; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for niacin the RDA is 130 percent of the EAR).

**RDA for Pregnancy**

<table>
<thead>
<tr>
<th>Age</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>18 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>19–30 years</td>
<td>18 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>31–50 years</td>
<td>18 mg/day of niacin equivalents</td>
</tr>
</tbody>
</table>

**Lactation**

**Method Used to Estimate the Average Requirement**

An estimated 1.4 mg of preformed niacin is secreted daily during lactation. Added to this is a small amount (1 mg) to cover energy expenditure involved in milk production. Thus, the additional amount of niacin needed is 2.4 mg/day of NEs for women who are exclusively breastfeeding an infant.

**Niacin EAR and RDA Summary, Lactation**

Adding 2.4 mg of NEs to the EAR of 11 mg of NEs for non-
pregnant, nonlactating women gives an EAR for niacin for lactation of 13.4 mg, rounded down to 13.

**EAR for Lactation**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>EAR (mg/day of niacin equivalents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>13 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>19–30 years</td>
<td>13 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>31–50 years</td>
<td>13 mg/day of niacin equivalents</td>
</tr>
</tbody>
</table>

The data in Table 6-1 suggest a CV for the niacin requirement that is greater than 10 percent. The wide variation in the efficiency of converting tryptophan to niacin may contribute to the larger apparent variation. Thus, a CV of 15 percent is used because information is not available on the standard deviation of the requirement during lactation; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for niacin the RDA is 130 percent of the EAR).

**RDA for Lactation**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>RDA (mg/day of niacin equivalents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>17 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>19–30 years</td>
<td>17 mg/day of niacin equivalents</td>
</tr>
<tr>
<td>31–50 years</td>
<td>17 mg/day of niacin equivalents</td>
</tr>
</tbody>
</table>

**Special Considerations**

The RDAs given above are not expected to be sufficient to meet the needs of persons with Hartnup’s disease, liver cirrhosis, or carcinoid syndrome or of those on long-term isoniazid treatment. As for other B vitamins, extra niacin may be required by persons treated with hemodialysis or peritoneal dialysis, those with malabsorption syndrome, pregnant women bearing multiple fetuses, and women breastfeeding more than one infant.

**INTAKE OF NIACIN**

**Food Sources**

Data obtained from the 1995 Continuing Survey of Food Intakes by Individuals indicate that the greatest contribution to the niacin intake of the U.S. adult population comes from mixed dishes high in meat, fish, or poultry; poultry as an entree; enriched and whole-grain breads and bread products; and fortified ready-to-eat cereals
(Table 6-2). In addition to the foods listed in Table 6-2, most flesh foods are sources of niacin, providing at least 2 mg per serving.

**Dietary Intake**

Niacin intake in the United States is generous in comparison with the Estimated Average Requirement (EAR). For example, the median intake by adult women is 17 to 20 mg of niacin (Appendixes G and H) in comparison with an EAR of 11 mg of niacin equivalents (NEs). (Survey data are reported as preformed niacin; no addition has been made for the conversion of tryptophan to niacin.) For all life stage and gender groups it appears that almost all individuals' usual niacin intakes would exceed the EAR if intake was expressed in NEs and thus the contribution of tryptophan was included. Intakes of niacin in two Canadian provinces are reported in NEs and are well above the EAR for all life stage and gender groups (Appendix I).

The Boston Nutritional Status Survey (Appendix F) indicates that this relatively advantaged group of people over age 60 has a median niacin intake of 21 mg/day for men and 17 mg/day for women, again, significantly above the EARs for adult men and women.

**Intake from Supplements**

Information from the Boston Nutritional Status Survey on the use of niacin supplements by a free-living elderly population is given in Appendix F. For those taking supplements, the fiftieth percentile of supplemental niacin intake was 20 mg for men and 30 mg for women. In the 1986 National Health Interview Survey, 26 percent of all adults reported use of supplements containing niacin (Moss et al., 1989). Supplements containing up to about 400 mg of niacin are available without a prescription.

**TOLERABLE UPPER INTAKE LEVELS**

**Hazard Identification**

**Adverse Effects**

There is no evidence of adverse effects from the consumption of naturally occurring niacin in foods. Therefore, this review is limited to evidence concerning intake of niacin as a supplement, food fortificant, or pharmacological agent.
### TABLE 6-2  
Food Groups Providing Niacin\(^a\) in the Diets of U.S. Men and Women Aged 19 Years and Older, CSFII, 1995\(^b\)

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Contribution to Total Niacin Intake(^c) (%)</th>
<th>Foods Within the Group that Provide at Least 4 mg of Niacin(^d) per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
<td>4–8 mg</td>
</tr>
<tr>
<td>Mixed foods(^e)</td>
<td></td>
<td>NA(^f)</td>
</tr>
<tr>
<td>Poultry</td>
<td>14.7</td>
<td>Turkey light meat, duck, and chicken light and dark meat</td>
</tr>
<tr>
<td>Bread and bread products</td>
<td>10.7</td>
<td>—</td>
</tr>
<tr>
<td>Ready-to-eat cereals</td>
<td>8.3</td>
<td>Moderately fortified</td>
</tr>
<tr>
<td>Mixed foods, main ingredient is grain</td>
<td>8.0</td>
<td>NA</td>
</tr>
<tr>
<td>Beef</td>
<td>6.5</td>
<td>—</td>
</tr>
<tr>
<td>Processed meats(^g)</td>
<td>4.7</td>
<td>—</td>
</tr>
</tbody>
</table>

**Niacin from other food groups**

| Vermont, veal, game                           | 0.4                                        | —                                                                          | Veal                                                                   |
| Organ meats                                   | 0.2                                        | —                                                                          | Liver                                                                   |

\(^a\) Preformed niacin only, not niacin equivalents.

\(^b\) CSFII = Continuing Survey of Food Intakes by Individuals.

\(^c\) Contribution to total intake reflects both the concentration of the nutrient in the food and the amount of the food consumed. It refers to the percentage contribution to the American diet for both men and women, based on 1995 CSFII data.

\(^d\) 4 mg represents 20% of the Recommended Daily Intake (20.0 mg) of niacin—a value set by the Food and Drug Administration.

\(^e\) Includes sandwiches and other foods with meat, poultry, or fish as the main ingredient.

\(^f\) NA = not applicable. Mixed foods were not considered for this table.

\(^g\) Includes frankfurters, sausages, lunch meats, and meat spreads.

One report showed adverse effects after consumption of bagels to which 60 times the normal amount of niacin had been added inadvertently (CDC, 1983). Most of the data on the adverse effects of excess niacin intake are from studies and case reports involving patients with hyperlipidemia or other disorders who were treated with pharmacological preparations containing immediate-release nicotinic acid or slow- or sustained-release nicotinic acid. The Tolerable Upper Intake Level (UL) developed here applies to all forms of niacin added to foods or taken as supplements (e.g., immediate-release, slow or sustained-release nicotinic acid, and niacinamide [nicotinamide]). Adverse effects such as nausea, vomiting, and signs and symptoms of liver toxicity have been observed at nicotinamide intakes of 3,000 mg/day (Rader et al., 1992) compared with intakes of nicotinic acid of 1,500 mg/day (McKenney et al., 1994). The generic term \textit{niacin} may be considered interchangeable with \textit{nicotinic acid}. As described below, the critical adverse effect selected was flushing to the extent that it results in a change in the dosing pattern or withdrawal from treatment.

\textit{Vasodilatory Effects (Flushing).} The term flushing covers a burning, tingling, and itching sensation as well as a reddened flush primarily on the face, arms, and chest. Flushing occurs in many patients treated with nicotinic acid therapeutically. It is often accompanied by pruritus, headaches, and increased intracranial blood flow (Miller and Hayes, 1982). Occasionally, it is accompanied by pain (Bean and Spies, 1940). Case reports and clinical trials have reported flushing effects at oral doses of 30 to 1,000 mg/day within 30 minutes to 6 weeks of the initial dose (CDC, 1983; Estep et al., 1977; Henkin et al., 1990; McKenney et al., 1994; Sebrell and Butler, 1938; Spies et al., 1938). Although flushing is a transient effect, it often results in patients deciding to withdraw from treatment.

In a study of the flushing effects of nicotinic acid and other pyridine compounds in humans, Bean and Spies (1940) suggest that pyridine compounds without a carboxyl radical in the 3 position of the pyridine ring do not produce flushing effects. Nicotinamide, which does not have a carboxyl radical in the 3 position, does not appear to be associated with flushing.

Flushing appears to be more closely related to a continuous rise in plasma nicotinic acid concentrations than to the absolute dose. Tolerance to nicotinic acid-induced flushing can develop whereby the effects are minimized when the dose is slowly increased over time (Stern et al., 1991). Flushing effects can also be reduced somewhat by taking niacin with food (Knodel and Talbert, 1987). Flush-
Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline

Gastrointestinal Effects. In addition to flushing, nonspecific gastrointestinal effects are common in patients treated with nicotinic acid (Knodel and Talbert, 1987), especially with slow-release preparations (McKenney et al., 1994; Rader et al., 1992). The gastrointestinal effects in patients taking the slow-release form have been shown to be associated with liver enzyme elevations (Gibbons et al., 1995).

Hepatotoxicity. The hepatotoxicity of niacin has been demonstrated in numerous case reports (Clementz and Holmes, 1987; Dalton and Berry, 1992; Einstein et al., 1975; Etchason et al., 1991; Ferenchick and Rovner, 1989; Frost, 1991; Goldstein, 1988; Henkin et al., 1990; Hodis, 1990; Knapp and Middleton, 1991; Knopp, 1991; McKenney et al., 1994; Mullin et al., 1989; Palumbo, 1991; Patterson et al., 1983). In the most severe cases, patients develop liver dysfunction and fulminant hepatitis and may progress to stage 3 and 4 encephalopathy requiring liver transplantation (Clementz and Holmes, 1987; Hodis, 1990; Mullin et al., 1989). The most frequently observed manifestations of niacin-induced hepatitis are jaundice and increased levels of serum transaminases (Etchason et al., 1991). These effects are typically associated with high doses (3 to 9 g/day of niacin) used to treat patients with hypercholesterolemia for periods of months to years (Clementz and Holmes, 1987; Einstein et al., 1975; Pardue, 1961; Patterson et al., 1983; Rivin, 1959; Winter and Boyer, 1973). Almost all of the patients in these case reports were taking the slow-release form. A recent double-blind comparison study suggested that the slow-release form is more hepatotoxic than the immediate-release form (McKenney et al., 1994). However, another study reported hepatotoxicity with both forms of niacin (Gray et al., 1994).

Glucose Intolerance. Large doses (3 g/day) of nicotinic acid used to treat patients with hypercholesterolemia have produced impaired glucose tolerance in otherwise apparently healthy individuals (Miettinen et al., 1969). The adverse effects on glucose tolerance have been observed during short- and long-term administration of the drug (Schwartz, 1993).

Ocular Effects. Niacin treatment may produce significant ocular effects, including blurred vision, toxic amblyopia, macular edema,
and cystic maculopathy. However, there are very few cases in the literature (Fraunfelder et al., 1995). Doses of 1.5 to 5 g/day of niacin have been associated with ocular effects (Fraunfelder et al., 1995; Gass, 1973; Millay et al., 1988). Niacin-induced ocular effects appear to be reversible and dose dependent.

**Summary**

Flushing is the adverse effect first observed after excess niacin intake and is generally observed at lower doses than are other effects. Flushing that results in patients deciding to change the pattern of niacin intake (i.e., reduce the amount taken at a time or withdraw from treatment) was selected as the most appropriate endpoint on which to base a UL. Although nicotinamide appears not to be associated with flushing effects, a UL for nicotinic acid that is based on flushing is considered protective against potential adverse effects of nicotinamide. The data on hepatotoxicity are considered less relevant to the general population because they involve large doses taken for long periods of time for the treatment of a medical condition.

**Dose-Response Assessment**

**Adults**

**Data Selection.** The data sets used to identify the lowest-observed-adverse-effect level (LOAEL) for niacin included anecdotal reports and clinical trials involving oral intake of niacin by healthy individuals. Studies involving parenteral administration were not considered in the dose-response assessment. Studies involving immediate-release forms of niacin were considered more relevant to niacin intake by the general population than were studies involving sustained-release forms.

**Identification of a LOAEL.** The data are not adequate to identify a no-observed-adverse-effect level (NOAEL) for flushing. To identify a LOAEL, flushing reactions were considered if they resulted in a patient either changing the form or amount of niacin used or withdrawing from treatment. A LOAEL of 50 mg/day was identified based on a study by Sebrell and Butler (1938) in which four (66 percent) of six persons experienced a flushing sensation after oral intake of 50 mg/day of nicotinic acid given with meals for 92 days. In one of the four subjects who experienced flushing effects, the
daily dose of 50 mg was given as 25 mg in the morning and evening. Although this study also reported a flushing reaction in one of six subjects taking 30 mg of nicotinic acid daily on day 32 of intake, this reaction was not bothersome enough to change the dosing pattern. Sebrell and Butler (1938) was selected as the critical study for identifying a LOAEL and deriving a UL because it provides the lowest effect level. A study by Spies et al. (1938) provides supportive evidence for a LOAEL of 50 mg/day. In this study, five of 100 individuals (5 percent) experienced flushing after a single oral dose of 50 mg of nicotinic acid, 50 individuals (50 percent) experienced flushing after 100 mg, and all individuals experienced flushing after 500 mg.

There is one case report showing that 14 of 69 persons (20 percent) experienced onset of rash, pruritus, and a sensation of warmth about 30 minutes after consuming one or more pumpernickel bagels to which niacin had been inadvertently added from an improperly labeled container (CDC, 1983). The bagels were found to contain an average of 190 mg of niacin.

**Uncertainty Assessment.** Because of the transient nature of the flushing effect, a small uncertainty factor (UF) of 1.5 was selected. A smaller UF was not appropriate because it is applied to a LOAEL rather than a NOAEL.

**Derivation of a UL.** A LOAEL of 50 mg/day was divided by a UF of 1.5 to obtain the UL for adults of 35 mg/day, a rounded estimate.

**UL for Adults 19 years and older 35 mg/day of niacin**

**Other Life Stage Groups**

For infants the UL was judged not determinable because of a lack of data on adverse effects in this age group and concern about the infant’s ability to handle excess amounts. To prevent high levels of intake, the only source of intake for infants should be from food. No data were found to suggest that other life stage groups have increased susceptibility to flushing effects from excess niacin intake. Therefore, the UL of 35 mg/day is also set for pregnant and lactating adult women. The UL of 35 mg/day for adults was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 3 and by using reference weights from Chapter 1, Table 1-2. Values have been rounded down.
### UL for Infants
0–12 months  Not possible to establish; source of intake should be formula and food only

### UL for Children
- 1–3 years  10 mg/day of niacin
- 4–8 years  15 mg/day of niacin
- 9–13 years  20 mg/day of niacin

### UL for Adolescents
- 14–18 years  30 mg/day of niacin

### UL for Pregnancy
- 14–18 years  30 mg/day of niacin
- 19 years and older  35 mg/day of niacin

### UL for Lactation
- 14–18 years  30 mg/day of niacin
- 19 years and older  35 mg/day of niacin

#### Special Considerations
A review of the literature identified individuals with the following conditions as being distinctly susceptible to the adverse effects of excess niacin intake: hepatic dysfunction or a history of liver disease, diabetes mellitus, active peptic ulcer disease, gout, cardiac arrhythmias, inflammatory bowel disease, migraine headaches, and alcoholism. Therefore, people with these conditions may not be protected by the UL for niacin for the general population.

#### Intake Assessment
On the basis of data from the Third National Health and Nutrition Survey, the highest mean intake of niacin from diet and supplements for any life stage and gender group was 39 mg/day. This intake was being consumed by men aged 31 through 50 years, women over age 70, and pregnant women aged 14 through 55 years. The highest reported intake at the ninety-fifth percentile was 77 mg/day in women aged 51 through 70 years (see Appendix H). Niacin is available over the counter in dosages ranging up to 100 mg or more (in the immediate-release form).
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Risk Characterization

Niacin intake data indicate that a small percentage of the U.S. population is likely to exceed the UL. Individuals who take over-the-counter niacin to treat themselves, for example, for high blood cholesterol, might exceed the UL on a chronic basis. The UL is not meant to apply to individuals who are receiving niacin under medical supervision.

RESEARCH RECOMMENDATIONS FOR NIACIN

Data useful for setting the Estimated Average Requirement (EAR) for children, adolescents, pregnant women, and lactating women are scanty, but evidence suggests that niacin intake in the United States and Canada is generous relative to need. Priority should be given to studies in two areas:

- the niacin requirement to satisfy nicotinamide adenine dinucleotide (NAD) needs for increased adenosine diphosphate ribosylation resulting from oxidant-deoxyribonucleic acid damage and
- sensitive and specific blood measures of niacin status. Current assessments of niacin status and requirement are based solely on urinary metabolite measures; measurements of plasma metabolites such as the 2-pyridone derivatives may be productive. Two recent experimental studies have suggested erythrocyte NAD as a functional blood measure of niacin status (Fu et al., 1989; Ribaya-Mercado et al., 1997), but further work is needed in clinical populations.

REFERENCES


Dietary Reference Intakes


