Supplementing Dietary Nutrients

A Guide for Healthcare Professionals

SECOND EDITION

Defining Optimal Nutrition • Nutrients as Genomic & Epigenetic Signals • Protein Supplementation
Fatty Acid Supplements • Vitamin Sources & Forms • Mineral Sources & Forms
Natural vs. Synthetic Vitamins • Whole Food vs. Isolates • Choosing a Probiotic
Botanical & Phytonutrient Basics • Fundamentals of Dietary Supplement Regulations
Deciphering Supplement Labels • Prenatal Supplementation • And Much More….

THE STANDARD
ROAD MAP SERIES

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Foreword by Jeffrey Bland, Ph.D.

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Foreword

I have been involved as a researcher and educator in personalized nutrition and dietary supplementation for the past forty years. Over these decades, the basic and clinical sciences that describe the mechanism of action of various micronutrients and their role in supporting functional physiology has evolved in both quantity and quality. With the development of nutrigenomics in the early 21st century the field exploded with new information; advances which were then closely followed by the developing understanding of nutritional epigenetics. It has challenged those in the field to keep up with all these advances without losing the foundational knowledge that had been historically developed surrounding the role of various dietary supplements in health and disease prevention since their discovery in the early 20th century.

It takes a remarkable person to undertake writing a comprehensive review that can serve as a resource guide for this extensive body of information. A person with great attention to detail, who understands human biochemistry and the role that nutrients play in its function, and who has the ability to look back and forward in the development of the wisdom that has been gained through the work of countless researchers and clinicians concerning the importance of dietary supplements in both personal and population health.

This is why the book *Supplementing Dietary Nutrients-A Guide for Healthcare Professionals* needed to be authored by a professional such as Dr. Thomas Guilliams, who fulfills all of these criteria. Dr. Guilliams is a nutrition researcher, educator, thought-leader, and trusted authority providing balanced information for health professionals on the appropriate use of dietary supplements in personalized health care. His decades of experience serves well in the way he has approached the organization and content of this amazing encyclopedia of "news to use"concerning dietary supplements.

This is a reference book that should be in the library of any health professional that has an interest in dietary supplements and their application to personalized health care. There is a timeless quality to this book, in the way that the information is presented and the documentation and support that underlies its content. The future will bring new discoveries and information on the role and application of dietary supplements in health care, but the content of this book provides a review of the core concepts and logic that defies age and will be useful for decades to come.

This book is truly a treasure for those who own it, in that it saves hours of searching for valuable information concerning the portfolio of nutrients that are included under the definition of dietary supplements. Dr. Guilliams has done us all a great favor in assembling this expansive body of information on dietary supplements and their clinical application in personalized health care.

Jeffrey Bland Ph.D.
Founder & President, Personalized Lifestyle Medicine Institute

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Chrononutrition: Nutrient Signals and Circadian Rhythm

Synchronizing circadian rhythms across all tissue types is key to coordinating nutrient availability with metabolic function.[i,ii] It is important to upregulate nutrient absorption to anticipate incoming food, as well as increase nutrient metabolic capacity to coordinate daily energy consumption with energy expenditure.[iii,iv] In order to maintain this synchrony, metabolic cells within the peripheral tissues (e.g., liver, kidney, muscle, adipose, etc.) maintain a 24-hour circadian cycle that controls key metabolic functions.[v-vii] This cycle is managed, internally, by an exquisite expression of transcription factors with various half-lives and interactions (i.e., clock genes).[viii] Peripheral clocks within different tissues are constantly re-synchronized by signals that come from the central clock in the hypothalamus. Ultimately, the light/dark cycle is the strongest external signal synchronizing circadian functions within the central clock; a signal which is transmitted through the suprachiasmatic nucleus (SCN) of the hypothalamus and transmitted to peripheral tissues, in part, through the glucocorticoid (i.e., cortisol) signaling of the HPA axis.[ix, x]

In the past several decades researchers have documented a growing number of bioactive signals that come from the diet, many of which promote health and prevent chronic disease. Included amongst this vast array of signals are those that regulate gene expression (i.e., nutrigenomic) and those that provide cellular energy. Recent discoveries have now shown that the quantity, types and timing of nutrient signals are also critical to help synchronize the metabolic circadian rhythm of cells.[xii, xiii] These important new discoveries are helping researchers piece together how subtle changes in nutrient content and timing have wide ranging effects on cellular function and the overall health of the organism.

Research investigating the influence of meal timing, especially intermittent fasting, time-restricted feeding and the consumption of breakfast, has shown a strong influence on circadian metabolic functions. While some of these influences have only been reported in animals, several human studies have been recently published that suggest changes to meal timing can affect metabolic circadian rhythms. For instance,

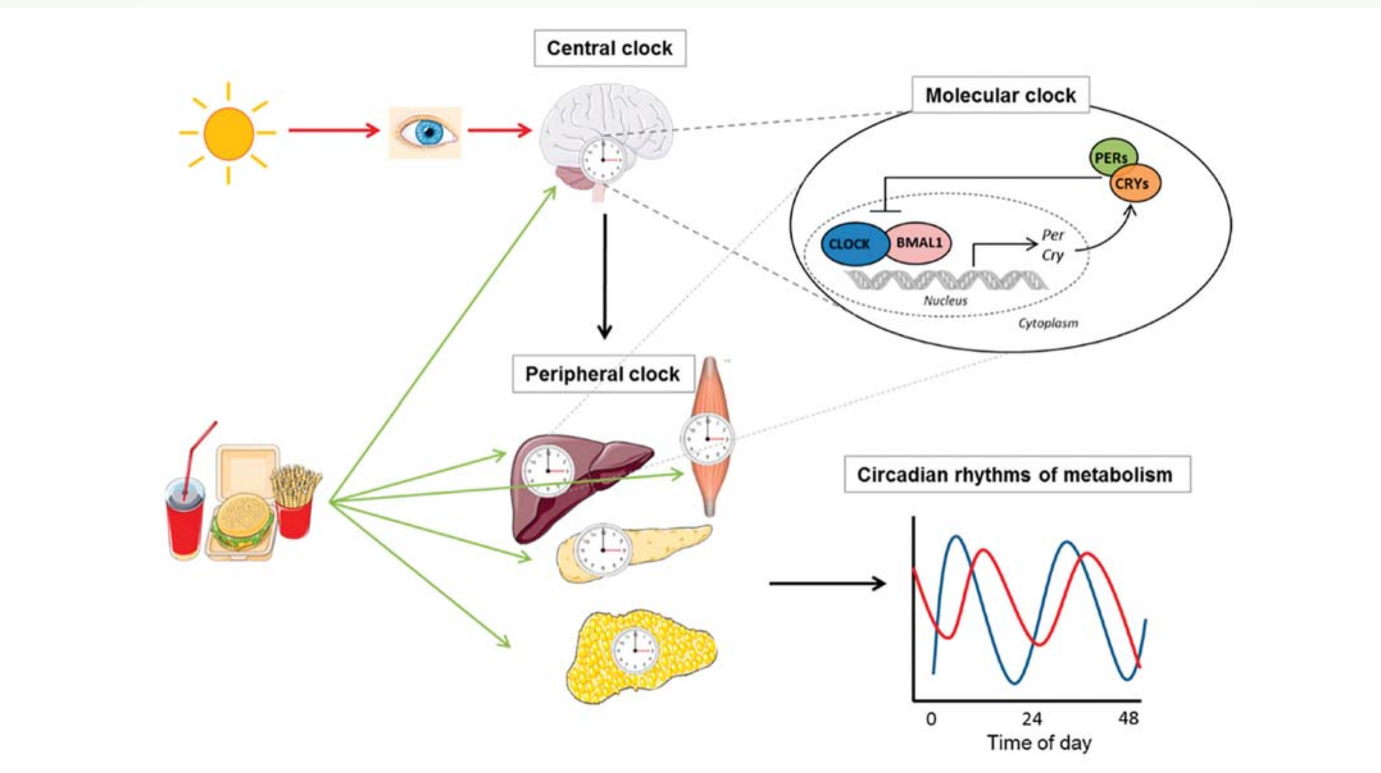


Figure 3: Circadian Regulation of Metabolism. In mammals, the circadian clock consists of a master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, which is synchronized by light/dark signals, and peripheral clocks, which is orchestrated by the master clock and controls metabolic rhythms. Food consumption can also entrain the endogenous clock but has a stronger influence on peripheral clocks than on the SCN. Image from *Int. J. Mol. Sci.* 2019, *20*(8), 1911.[xi]

Comparing Nutrient Forms: When are they Clinically Meaningful?

The world of nutrition and nutrient supplementation is full of marketing claims about the relative benefit or superiority of one form of a nutrient over another. Natural vs. synthetic, activated forms vs. precursors, better solubility, better absorption, the ability to cross the blood-brain barrier, and less side effects are just some of the claims being made. In this section we'll discuss a few of these issues, some of which can be quite contentious within the world of marketing vitamins and minerals. We will focus primarily on the basic differences and benefits between various forms of vitamins and minerals, leaving the nuanced discussion of each nutrient to their respective monograph (for a discussion of omega-3 fatty acid differences, see page 69). As it turns out, almost every vitamin and mineral used in food fortification or dietary supplements can be delivered in a variety of chemical forms.

In some cases, this might mean different isomers of the same molecule (e.g., natural RRR-α-tocopherol vs. synthetic R-S forms of vitamin E), a chemically similar bioequivalent molecule (e.g., riboflavin-5-phosphate vs. free riboflavin) or minerals compounded with different anions (e.g., calcium carbonate vs. calcium citrate). Further attempts to define nutrients based upon their supposed origins: *"whole-food," "natural concentrate," "active-form"* or *"synthetic"* create an additional level of differentiation. Unfortunately, these terms have different meanings to different people, and for the most part, are often used to mislead consumers about the benefit or harm of a nutritional supplement. Here, we will attempt to provide clear definitions of each of these terms, revealing the real potential differences between some nutrient forms, while suggesting that most marketing information about these differences is unsubstantiated, misleading and, in some cases, simply false.

Synthetic vs. Natural Vitamins

Few terms are more loaded with implied meaning in the supplement world as the words *"natural"* and *"synthetic."* The former is, quite naturally, nearly always viewed as being better than the latter. Many supplement users would be surprised to learn that nearly all vitamins and minerals used for making dietary supplement products—and for food fortification—are not *"natural"* by most people's definition (even if they are marketed as such). By this we mean that the nutrient ingredient, as it is actually used in the capsule, tablet or powder, has been altered in some way (besides merely being concentrated) from that nutrient's form as it is found in nature or has been *"synthesized"* from a different starting material to produce a bioidentical or bioequivalent molecule (more on these terms later). While this process usually involves a stepwise series of controlled chemical reactions, it often involves the biological activity of certain bacteria or yeast in the process (usually referred to as fermentation).

Many clinicians are already familiar with the use of bioidentical compounds in clinical practice when they use bioidentical hormones (e.g., progesterone). These compounds are chemically identical to the hormone produced in the human body but are synthetically derived from other (often natural) starting materials. For instance, bioidentical progesterone can be synthesized via the Marker reaction starting with the naturally-sourced ingredient diosgenin from wild yams (a 5-step process involving numerous intermediates and additional chemicals, see Figure 6). However, unlike nutrients that are intended to be taken orally, bioidentical hormones may have different levels of bioequivalence since these products need to be delivered through oral, transdermal or intravaginal routes — an unnatural delivery for endogenous hormones.

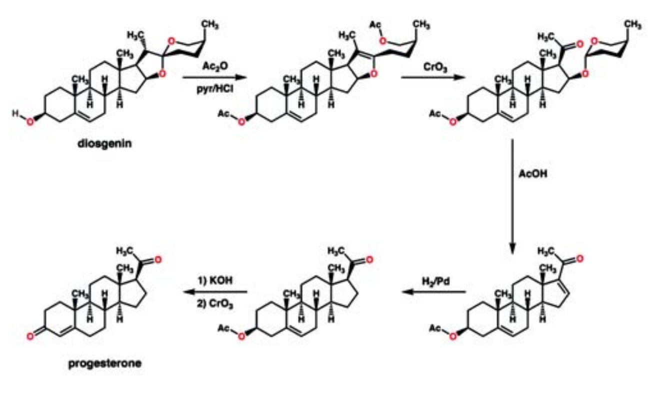


Figure 6: The Marker Degradation Reaction. This figure shows the five-step process for synthesizing progesterone from diosgenin, isolated from wild yams. This reaction was given its name from its developer, Russell Marker, in 1940. *J. Am. Chem. Soc.* 1940, 62, 9, 2525-2532.

Sources of Marine Omega-3 Ingredients

For the most part, the marine omega-3 fatty acid category is dominated by products best described as "fish oil"—that is, while there are products available that deliver n-3 fatty acids from other marine sources, nearly all the available research has been done with fish oil-derived fatty acids. These data using fish oil have become the benchmark for efficacy and safety and are the standard to which we compare other sources. While pharmaceutical products often avoid the use of the term "fish oil," these products are currently all made from fish-derived fatty acids.

The following are the main sources of marine omega-3 fatty acids:

- **Fish Body Oil:** The largest biomass used to create marine-derived n-3 fatty acids are small oily fish caught in the cold waters off the coast of Chile and Peru. The fish species most commonly used are anchovies and sardines, with some mackerel. Concentrations of these purified oils are the most common therapeutic ingredient used in dietary supplements and pharmaceutical products throughout the world. Other species used to produce fish oil may include salmon, tuna, menhaden, herring, cod and other minor species. The EPA and DHA (and other fatty acids) content, which is predominantly in the triglyceride form, is dependent on the species of fish, the water temperature, and other seasonal variables.
- **Cod Liver:** As a byproduct of the cod meat market, cod livers are used to provide a blend of fatty acids similar to unconcentrated fish body oil. Cod liver may also be a natural source of vitamins A and D.
- **Krill:** These small crustaceans feed on plankton and are subsequently eaten by many marine mammals, especially penguins and whales. Factory ships process krill immediately upon capture off the coast of Antarctica. Krill oil, which predominantly contains n-3 fatty acids in a free fatty acid and phospholipid form, is relatively low in EPA and DHA, but contains small amount of the carotenoid astaxanthin.
- **Calamari:** A more recent, but small, player in the n-3 fatty acid industry is calamari or squid oil. This oil, which is predominantly in the triglyceride form, has a higher ratio of DHA over EPA than typical fish oil. This material is a byproduct of the calamari food industry.
- **Mussels:** Shellfish are only a minor source of commercially available n-3 fatty acids. Nonetheless, several products are currently available from the fatty acids derived from Green-Lipped Mussels (*Perna canaliculus*).
- **Algae:** Various species of algae are commercial sources for n-3 fatty acids. Algae can be grown in large inland production sites where access to sunlight is plentiful. These products are predominantly in the triglyceride form and are very high in DHA, with only small amounts of EPA. Most of the pure DHA raw materials, especially pure DHA used for the fortification of infant formula, is sourced from algae. In addition, algae are currently the only vegan source of DHA available.
- **EPA and DHA from Genetically-Modified Plants:** Various algae, plants, and fungi have been genetically modified to produce various fatty acids, including both EPA and DHA. These ingredients are designed to help increase the global supply of these fatty acids, while limiting the harvesting burden on marine animals. As of 2018, these ingredients were only being produced for the supplementation of farm-raised fish (not directly used in dietary supplement ingredients).[16,17] It is possible these plant-derived EPA and DHA fatty acids may be approved for direct human consumption in the future.

Delivery Forms for Supplementation

When fatty acids are harvested from their source, they are typically in the form of triglycerides (TG), phospholipids (PL), or free fatty acids (FFA) and are relatively low in total EPA and DHA (< 30%). When consuming fish or unconcentrated fish oil (i.e., fish body oil or cod liver oil), these fatty acids are in the TG form, as they are in most plant and animal sources of fat. However, since the recommended doses of EPA and DHA are often difficult to consume using unconcentrated oils, several steps can be used to increase the EPA and DHA concentration of the product while increasing the purity of the fatty acids delivered. The EPA and DHA fatty acids can be removed from their glycerol backbone and separated from other fatty acids (via hydrolysis and distillation). These fatty acids are then concentrated as ethyl esters (EE) of EPA and DHA. These concentrated fatty acids can be re-attached to a glycerol backbone to form re-esterified TG (rTG) molecules which contain a much higher concentration of EPA and DHA compared to the original TG molecule. These two forms of concentrated fish oil (EE and rTG) are the most common sources used in clinical trials and often recommended by physicians (as dietary supplements or pharmaceuticals). It is important to note the distinctions between the various delivery forms of these fatty acids, as this often impacts their bioavailability and efficacy.

Vitamin B_2 (Riboflavin)

Essential Nutrient Functions

Riboflavin, also known as vitamin B_2, is a water-soluble B vitamin. In the body, riboflavin is primarily utilized as an integral component of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Coenzymes derived from riboflavin are termed flavocoenzymes, and enzymes that use a flavocoenzyme are called flavoproteins. These coenzymes act as electron carriers in a number of oxidation-reduction (redox) reactions involved in energy production and in numerous other metabolic pathways. Riboflavin-derived coenzymes are often used in metabolic processes that require vitamin B_2, folate, niacin and iron. Common food sources of riboflavin include wheat flour and bread, milk, eggs, almonds, chicken, beef and spinach.

Supplemental Forms

- **Free riboflavin**
- **Riboflavin-5-phosphate (R5P)/Flavin mononucleotide (FMN)**
- **Flavin adenine dinucleotide (FAD) from food sources**

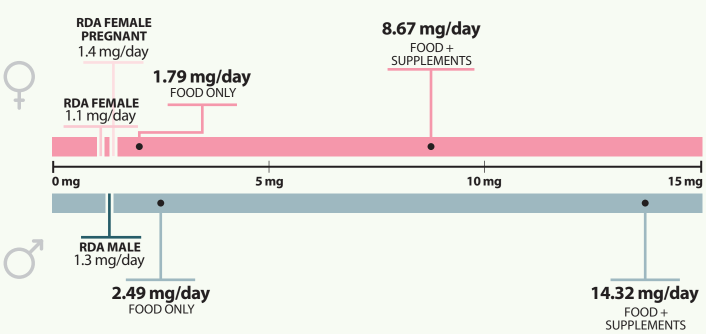
Vulnerabilities to Nutrient Inadequacy

Risk of Inadequate Intake

LOW | moderate | high

Standard American Diet: The risk of inadequate riboflavin intake is relatively low considering intakes from all food sources (2.9% below EAR). However, excluding enriched/fortified foods creates a moderate risk of inadequate riboflavin intake from naturally occurring sources alone (13.1% below EAR).

Average Intakes Compared to RDA from NHANES 2015 - 2016 for Individuals ≥ 20 Years



Additional Vulnerable Populations

Life Stage: Pregnant, lactating women and their infants (related to diet)

Lifestyle: Vegetarians and/or vegans (especially in certain life stages like in pregnant and lactating women and their infants), athletes

Conditions: Alcohol abuse

Drug-Induced Depletion: Amitriptyline (tricyclic antidepressants, TCAs), oral contraceptives

Lab Tests for Nutrient Status

- Erythrocyte glutathione reductase activity coefficient (EGRAC)
- Urinary fluorometric riboflavin excretion
- Plasma/serum/erythrocyte riboflavin

Special Notes

- Most animal and plant food sources contain at least a small amount of riboflavin.
- Riboflavin is easily destroyed upon exposure to light.

Recommended Intakes

The Dietary Reference Intakes (DRIs) for riboflavin are based on the prevention of riboflavin deficiency.[1,2,3] According to the Food and Nutrition Board of the IOM, several indicators of riboflavin status (sometimes used in combination) were used to establish the riboflavin DRIs (e.g., erythrocyte glutathione reductase, erythrocyte flavin concentration and urinary excretion of the vitamin in fasting, random, or 24-hour specimens or by load tests). Adequate Intakes (AIs) for infants were established as there was insufficient data available surrounding dietary riboflavin response to determine an RDA in this age group. As such, the AIs were based on the mean riboflavin intake of infants fed principally with human milk from well-nourished mothers who were not taking dietary supplements. The Daily Values (DVs) for riboflavin, set by the FDA, have recently decreased for children and adults > 4 years from 1.7 mg/day to 1.3 mg/day.

Riboflavin Intake Guidelines (mg/day)

	RDA		DV
Age	Males	Females	All Individuals
0-6 mos	0.3 (AI)	0.3 (AI)	0.4
7-12 mos	0.4 (AI)	0.4 (AI)	
1-3 yrs	0.5	0.5	0.5
4-8 yrs	0.6	0.6	1.3
9-13 yrs	0.9	0.9	
14-18 yrs	1.3	1.0	
Adults 19+ yrs	1.3	1.1	
Pregnancy/Lactation 14+ yrs		1.4/1.6	1.6

Vulnerabilities to Inadequate Riboflavin Status

Consuming the Standard American Diet

NHANES data (2015 - 2016) show that men and women (≥ 20 years) who are supplementing riboflavin get 14.32 mg and 8.67 mg/day, respectively, amounts considerably higher than the RDAs for each group (RDA for men and women is 1.3 and 1.1 mg/day, respectively).[4] This compares to non-supplement users where men get 2.49 mg riboflavin and women consume 1.79 mg/day riboflavin, showing that even without supplementation, on average, both men and women meet the RDA for estimated intake from food sources (which includes enriched and fortified foods). Interestingly, when NHANES dietary intake data from 2009 - 2012 were further differentiated, food enrichment and fortification were shown to play a large role in the relatively low prevalence of subjects below the EAR for reported riboflavin intake.[5] Specifically, 13.1% of the NHANES population ≥ 2 years reported riboflavin intakes below the EAR when naturally-occurring food sources were considered, which was reduced to 2.9% of the population below the riboflavin EAR when enriched/fortified food sources of riboflavin were considered alongside the naturally occurring sources and was further reduced to 2.4% of the population when dietary supplements were included in addition to riboflavin from food sources (i.e., naturally occurring, enriched and fortified sources). Similarly, an analysis of NHANES data from 2003 - 2006 echoed these results, suggesting that the enrichment/fortification of foods plays a large role in the relatively low prevalence of subjects below the EAR for reported riboflavin intake.[6] Most foods (from animal and plant sources) have some small quantities of riboflavin, making it relatively simple for both men and women to reach the riboflavin RDA. More so, foods such as wheat flour and bread products have been enriched with riboflavin (among other nutrients) since 1943.

Although the above NHANES data from the United States suggest the prevalence of inadequate reported riboflavin intakes is relatively low (especially in those consuming enriched/fortified foods and/or using dietary supplements), one study found an unexpected high prevalence of suboptimal or deficient riboflavin status using a functional measure of riboflavin status (i.e., erythrocyte glutathione reductase activity coefficient (EGRAC)) in a convenience sample of women from Vancouver, Canada (N = 49, ages 20 - 45 years).[7] It was discovered that 69% of these Vancouver women had a suboptimal or deficient riboflavin status as defined as EGRAC ≥ 1.3.[7] The authors speculate that the lack of consuming riboflavin-rich dairy products may explain this phenomenon. Although interesting, these data are from a small epidemiological study, so it is difficult to generalize these findings outside this specific group of women. Nevertheless, these data act to remind the clinician that vitamin status based on estimated food intake may not adequately reflect actual vitamin status or activity. Frank riboflavin deficiency has a higher prevalence in some developing countries.[7]

Life Stages Predisposing to Inadequate Riboflavin Status

Pregnant or lactating women who are strict **vegetarian/ vegan**, and consequently their **infants**, are vulnerable to inadequate riboflavin status - see below.

Lifestyle Factors Predisposing to Inadequate Riboflavin Status

Vegetarians/Vegans: Pregnant or lactating women in the United States who are practicing vegetarians or vegans who do not regularly consume dairy or meat products are susceptible to possible riboflavin deficiency.[2] In addition, newborns of riboflavin deficient mothers carry a greater risk of deficiency and birth defects, although the evidence is mixed.[8,9] Furthermore, vegetarians and vegans who consume very little or absolutely no dairy or meat products, which contribute significantly to most riboflavin intake, are at increased risk of riboflavin deficiency. Rates of riboflavin deficiency among vegetarians and vegans ranged from 10% to nearly 50% in studies conducted in the early 2000s.[10,11]

Athletes: It is the position of the American Dietetic Association, Dieticians of Canada and the American College of Sports Medicine that athletes are at increased risk of developing nutrient deficiencies, such as riboflavin deficiency, due to the increased need of this vitamin to support vigorous exercise.[12] However, in the updated position statement by these organizations riboflavin, specifically, was not mentioned.[24] Vegetarian and vegan athletes, who avoid foods that are great sources of riboflavin (e.g., milk, eggs, meat and cheese), are even more vulnerable to riboflavin deficiency.[12]

Health Conditions Predisposing to Inadequate Riboflavin Status

Alcohol Abuse: Individuals who suffer from alcohol abuse frequently struggle to consume adequate intakes of many nutrients, including riboflavin. In addition, excessive riboflavin excretion and impaired intestinal absorption may occur which also contributes to a suboptimal riboflavin status.[13] In rats chronically fed alcohol, riboflavin transporters were inhibited and caused impairment in intestinal absorption and re-uptake of the vitamin from the kidneys.[14]

Drug-Induced Nutrient Depletion

Amitriptyline (tricyclic antidepressants, TCAs): The chemical structure of amitriptyline is similar to the structure of riboflavin and therefore, was speculated to have inhibitory effects on riboflavin function. In 1981, Pinto et al. investigated whether riboflavin was inhibited by amitriptyline in adult male rats by separating the rats into groups based on which psychotropic agent was administered. Rats in the amitriptyline group showed a significant decrease in flavokinase activity, the first of two enzymes in the conversion of riboflavin to its active coenzyme derivative, flavin adenine dinucleotide (FAD).[15] Coadministration of riboflavin may augment the therapeutic activity of TCAs, although research on this topic is limited.[16]

Oral Contraceptives: Oral contraceptives (OC) are commonly used by women of reproductive age for birth control. Previously, the World Health Organization recognized the importance of understanding the influence that OC drugs have on nutrient requirements. Several studies, which date back to the 1970s, have investigated this potential relationship but the findings are mixed. One study showed that women with low socioeconomic status were at increased risk for developing a riboflavin deficiency and that the use of OC exasperates this prevalence, although many drawbacks to this study were noted.[17] In contrast, a different study showed that when dietary intake of riboflavin was controlled, OC use did not significantly alter riboflavin status.[18] There are several other studies that show mixed results, but altogether, the findings suggest that oral riboflavin supplementation may be a cost-effective and beneficial intervention to support nutrient status in those where nutrition is poor and OC are used.

Lab Tests for Nutrient Status

Riboflavin status is typically not measured in healthy individuals; however, some assays are available for approximating riboflavin status.[2]

Erythrocyte Glutathione Reductase Activity Coefficient (EGRAC): An effective functional assay of riboflavin status is the erythrocyte glutathione reductase activity coefficient (EGRAC), which evaluates the adequacy of riboflavin to function as a cofactor in this enzymatic reaction by studying the ratio between the enzyme's activity with and without the *ex vivo* addition of the cofactor FAD.[19] An EGRAC coefficient > 1.4 indicates a riboflavin insufficiency and < 1.2 indicates an adequate status.[3,20] In a 2009 systematic review, the EGRAC was found to be an effective biomarker for assessing altered riboflavin intake (P < 0.00001), compared to 13 other biomarkers.[21] This biomarker cannot be used in individuals with glucose-6-phosphate dehydrogenase deficiency, as low riboflavin concentrations may be a consequence of this condition.[2]

Urinary Fluorometric Riboflavin Excretion: Assessing riboflavin status by urinary fluorometric riboflavin excretion is used mostly for determining dietary intake within a population, rather than in an individual. Urinary riboflavin excretion is an indirect measure of riboflavin status, where a rate of < 40 μg/day is indicative of deficiency.[2] This is usually measured over a 24 hour period as the total amount of riboflavin excreted, or this measure is standardized to the amount of creatine excreted.[2] This test strongly reflects dietary riboflavin intake, whereas EGRAC is a more accurate measure of long-term riboflavin status.[2]

Serum/Plasma, Erythrocyte or Whole Blood Riboflavin: It is challenging to assess the usefulness of plasma, serum, erythrocyte and whole blood biomarkers of riboflavin status because only a few studies with heterogeneous study designs and assay preparations have been completed for each.[21] Nevertheless, in 2002, Hustad et al. investigated the relationship between EGRAC, plasma, and erythrocyte concentrations of riboflavin and its cofactors, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) in 46 elderly individuals. The authors concluded that all vitamers except plasma FAD are potential indicators of riboflavin status.[19] Another study compared erythrocyte riboflavin concentrations with EGRAC in pregnant Nepali women (N = 84) and found the deficiency level of erythrocyte riboflavin associated with EGRAC deficiency levels (defined as ≥ 1.4) was 164 nmol/L and had both a sensitivity and specificity of 82%.[20] In short, the available research gives limited data to support the use of these aforementioned assays in assessing riboflavin status, and reference ranges for serum/plasma, erythrocyte and whole blood riboflavin differ depending on the lab providing the test. Despite the limited data supporting serum/plasma, erythrocyte and whole blood assays as estimates of riboflavin status, the research seems to provide a general consensus that the erythrocyte glutathione reductase activity coefficient is the biochemical indicator of choice for riboflavin assessment (see above).

Symptoms of Riboflavin Deficiency

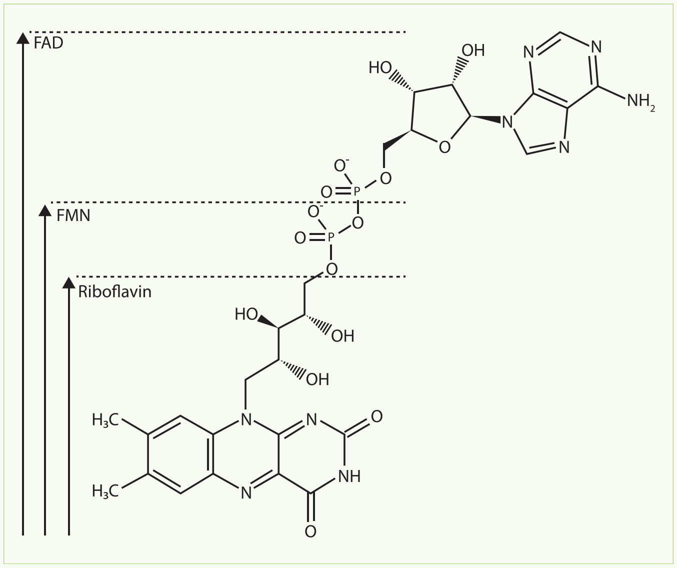
As mentioned, riboflavin deficiency (also known as ariboflavinosis) is rare in the United States and is usually associated with the concurrent deficiency of other nutrients.[1,2,3] Riboflavin deficiency is characterized by the following signs and symptoms: sore throat, hyperemia (excess blood), edema of the mouth and throat, lesions in the corner of the mouth (angular stomatitis), swollen/cracked lips (cheilosis), inflammation/redness of the tongue (magenta tongue), scaly skin inflammation (seborrheic dermatitis), hair loss, reproductive problems, itchy/red eyes and degeneration of the liver and nervous system. Severe riboflavin deficiency may also impair the metabolism of other nutrients which depend on flavin coenzymes (e.g., the conversion of vitamin B_6 to its coenzyme form and the conversion of tryptophan to functional forms of niacin). With severe and prolonged riboflavin deficiency, anemia and cataracts may develop.

Potential for Toxicity

There are no known toxic effects or adverse reactions related to riboflavin and the IOM lists no upper limit for riboflavin intake. Moderate to high-dose riboflavin therapy has been found to intensify urine color to a bright yellow (flavinuria), which is a harmless side effect.[1]

Supplemental Forms

Riboflavin is naturally found in foods as either free riboflavin or one of its coenzyme derivatives (FAD/FMN). The bioavailability of these compounds is similar since each form is hydrolyzed to free riboflavin prior to transport into the body.[22] Dietary supplements typically contain either the synthetic *"bioidentical"* riboflavin or the synthetic derivative called riboflavin monophosphate (riboflavin-5-phosphate, R5P). Riboflavin-5-phosphate is often marketed as an *"activated"* or natural form of riboflavin. As it turns out, this synthetic form, also a *"bioidentical"* form, must be dephosphorylated prior to transport into the body. This has been known since the mid-1960s.[23] We are unaware of any study that has attempted to compare the clinical differences between oral supplementation of free riboflavin with R5P; and unless R5P has an undocumented effect within the gastrointestinal lumen prior to being hydrolyzed to free riboflavin, no clinical difference would be anticipated (whether intravenous supplementation of these different forms results in clinically different outcomes is also not known). While no evidence suggests that R5P is an inferior form of the vitamin compared to free riboflavin, it is substantially more expensive.



Chemical Structures of Riboflavin, Flavin Mononucleotide (FMN) and Flavin Adenine Dinucleotide (FAD). Figure modified from: Huijbers M, Martínez-Júlvez M, Westphal A, Delgado-Arciniega E, Medina M, Berkel W. Proline dehydrogenase from Thermus thermophilus does not discriminate between FAD and FMN as cofactor. *Sci Rep.* 2017;7:43880.

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Vitamin B₃ (Niacin)

Essential Nutrient Functions

Niacin, or vitamin B_3, is a water-soluble vitamin that includes nicotinic acid and niacinamide, equivalent as vitamers though not for all therapies (see below). Niacinamide, or nicotinamide, is converted in the body to the metabolically active coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These active coenzymes are used in over 400 redox-related metabolic reactions vital for the basic functions within cells. Niacin is not technically an essential nutrient, as the body can produce niacinamide from the amino acid tryptophan, but it is functionally essential in most humans. Animal and plant food sources of niacin include beef, poultry, fish, nuts, legumes and grains.

Supplemental Forms

- **Nicotinic acid**
- **Niacinamide**
- **Niacinamide ascorbate**
- **Inositol hexanicotinate (IHN)**
- **Nicotinamide riboside**

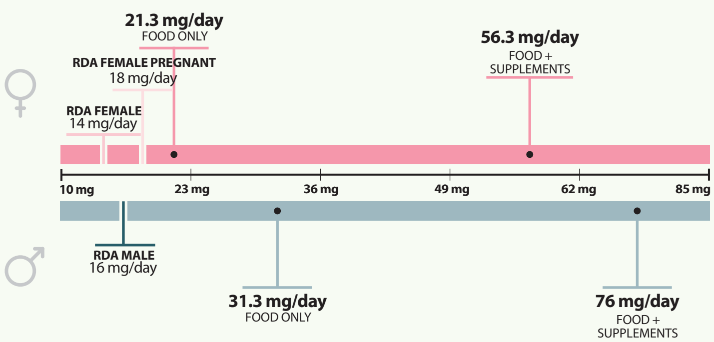
Vulnerabilities to Nutrient Inadequacy

Risk of Inadequate Intake

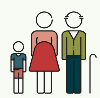
LOW | moderate | high

Standard American Diet: The risk of inadequate intake is low. NHANES data (2009 – 2012) found 1.2% of the population consume less than the EAR from enriched/fortified foods, however, risk increases from intake of naturally occurring food sources only.

Average Intakes Compared to RDA from NHANES 2015 - 2016 for Individuals ≥ 20 Years



Additional Vulnerable Populations



Life Stage: N/A

Lifestyle: N/A

Conditions: Alcohol abuse, Hartnup disease, carcinoid syndrome

Drug-Induced Depletion: Isoniazid

Lab Tests for Nutrient Status

- Serum/plasma niacin
- Urinary N1-methyl-nicotinamide and Urinary N1-methyl-2-pyridone-5-carboxamide
- Erythrocyte nicotinamide adenine dinucleotide (NAD)

Special Notes

- Although the FDA has approved various products containing niacin as lipid-altering drugs, niacin products of similar doses and clinical benefit, even some sold as delayed-release, can be legally sold as dietary supplements as long as the manufacturers and distributors make no disease or drug claims.

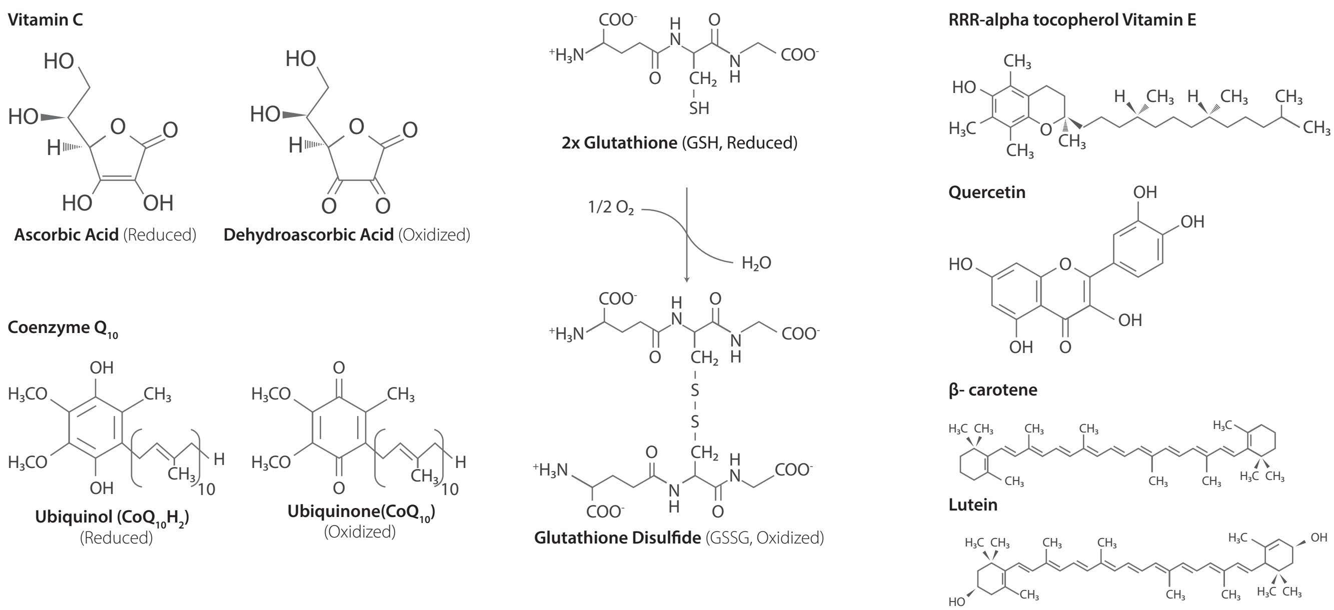


Figure 12: Chemical Structures of Direct Antioxidants. Please note that the reduced/oxidized forms are shown for vitamin C, glutathione and coenzyme Q_{10}. Structures are also shown for RRR-alpha tocopherol, quercetin, beta-carotene and lutein. See text for additional details.

Glutathione

The reduced form of glutathione (GSH) is a critical intracellular antioxidant molecule, though it is simply a tripeptide containing the amino acids L-glutamate, L-cysteine, and glycine (see Figure 12).[16] This small peptide functions as a direct intracellular antioxidant that scavenges free radicals, but also functions as a substrate for glutathione peroxidase (GPx) and glutathione transferase (GST) in their reactions to quench peroxides. GSH also reduces oxidized glutaredoxin (Grx), which is necessary for the reduction of disulfides. Therefore, maintaining an appropriate reduced/oxidized glutathione (GSH/GSSG) ratio is critical for cell vitality. When GSH levels are too low, the reduced cellular redox status may alter redox-dependent regulation of genes and have direct pathological consequences.[17-19] Finally, S-glutathionylation of certain proteins is a critical regulatory mechanism in metabolic activities requiring reversible modification of sulfhydryl groups of proteins using either GST or Grx.[20,21]

Since glutathione is such an important intracellular antioxidant and regulatory molecule, researchers have looked at many possible ways to increase its synthesis or improve the relative amount of its reduced form (GSH) in hopes of improving the overall antioxidant/redox capacity of the body and reduce aging and chronic disease. One obvious way would be to directly consume glutathione through the diet or by using glutathione supplements. However, many factors influence the way in which dietary compounds influence GSH levels, and direct consumption of glutathione in foods may have little impact on whole body GSH levels, though diets with high levels of fresh fruits and vegetables (i.e., Mediterranean diet) have been shown to increase GSH levels.[22-24]

The efficacy of improving glutathione status using oral supplementation of glutathione in capsules or tablets is a hotly debated topic. For many years, oral supplementation of L-glutathione appeared to have little impact on measures of glutathione status, leading many to conclude that the tripeptide is easily destroyed in the stomach and/or has poor absorption in the gut. However, a recent study showed that oral supplementation of pure L-glutathione can significantly increase GSH levels in whole blood, plasma, lymphocytes and RBCs in a dose-dependent manner.[25] The study was performed in 61 healthy subjects given placebo, 250 mg L-glutathione/day or 1,000 mg L-glutathione/day for 6 months, having their GSH status measured at baseline, and after 1, 3, 6 and 7 months (one month post-supplementation). While both doses increased GSH levels in most samples measured, the 1,000 mg dose had a much greater and statistically significant increase, compared to the 250 mg dose. Despite this recent study, others contend that liposomal forms of L-glutathione are necessary to achieve meaningful absorption when taken orally, though human clinical studies designed to compare these forms are limited.[26] Supplemental L-glutathione is commercially produced by providing various reagents (e.g., glucose, glycine, thiosulfate, etc.) to microbes that synthesize glutathione (e.g., yeast, bacteria) through fermentation, where it can be subsequently purified and crystalized in large batches for use in manufacturing capsules and tablets.

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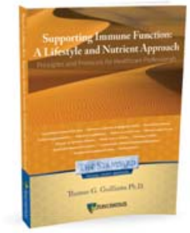

Supporting Immune Function: A Lifestyle and Nutrient Approach
Principles and Protocols for Healthcare Professionals

This Road map summarizes the latest knowledge concerning clinically-relevant immune system function (including autoimmune dysfunctions). Evidence for lifestyle and nutrient interventions affecting immune functions are discussed in detail; along with suggested protocols for improving immune function related to both acute and chronic immune challenges.

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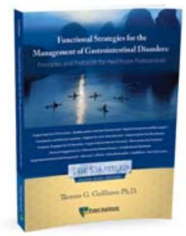
This Road map outlines the evidence connecting HPA-axis and stress-related dysfunction with a wide-range of chronic diseases. Different testing and protocol strategies are reviewed, allowing the clinician to design a diagnostic and treatment strategy that suits their practice and patients. Intervention strategies emphasize lifestyle, nutritional and nutraceutical therapies.



Functional Strategies for the Management of Gastrointestinal Disorders
Principles and Protocols for Healthcare Professionals

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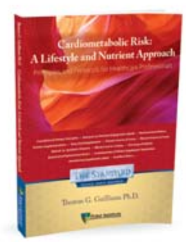
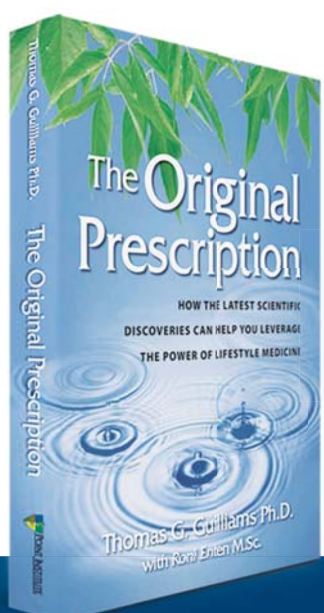


Cardiometabolic Risk: A Lifestyle and Nutrient Approach
Principles and Protocols for Healthcare Professionals

This Road map discusses the relationship between lifestyle inputs and the mechanisms that drive both type 2 diabetes and cardiovascular events. Strategies to help assess patient's insulin resistance, inflammatory status and lipid metabolism are coupled with evidence-based implementation strategies that include diet, exercise, stress-control and nutraceutical interventions.



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The use of dietary supplements continues to grow and is a fundamental health-promoting strategy to bridge the gap between a person's nutritional needs and their actual dietary intake. In addition, thousands of forward-thinking healthcare professionals routinely recommend dietary supplements to optimize their patient's nutrient status. However, clinicians and patients are routinely faced with an onslaught of confusing, contradictory, over-hyped and often misleading information about nutrition, especially dietary supplementation, preventing them from fully leveraging the potential of dietary supplementation. Unfortunately, many nutritional guideline recommendations and references are decades old and out-of-sync with the latest nutritional research; and most lack the practical and clinically-relevant relationship linking the evidence-based science of nutrition with the actual ingredients and products available to consumers in the real world. *Supplementing Dietary Nutrients—A Guide for Healthcare Professionals - Second Edition* continues to bridge this gap.

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- **Health Coaches**
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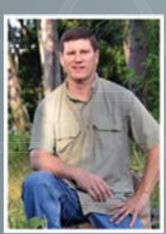

Thomas G. Guilliams Ph.D. earned his doctorate from the Medical College of Wisconsin (Milwaukee) where he studied molecular immunology in the Microbiology Department. Since 1996, he has spent his time studying the mechanisms and actions of natural-based therapies, and is an expert in the therapeutic uses of nutritional supplements. As the Vice President of Scientific Affairs for Ortho Molecular Products, he developed a wide array of products and programs which allow clinicians to use nutritional supplements and lifestyle interventions as safe, evidence-based and effective tools for a variety of patients. Tom teaches at the University of Wisconsin-School of Pharmacy, where he holds an appointment as a Clinical Instructor; and at the University of Minnesota School of Pharmacy. He lives outside of Stevens Point, Wisconsin with his wife and children.

Dr. Guilliams' other writings can be found at The Point Institute www.pointinstitute.org

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