

Twice Daily Multi™



A novel concept in defining levels and forms of supplemental vitamins and minerals

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Twice Daily Multi™ (TDM) is a two-a-day multivitamin designed to provide nutrients that are difficult to obtain in the typical daily diet. Its formulation has been guided by principles of evolutionary biology and human physiological adaptation to a whole food, nutrient-dense diet that supplies adequate energy, guided additionally by common nutrient insufficiencies in the US and by criteria beyond the established Recommended Dietary Allowances (RDAs) and Adequate Intakes (AIs).

TDM includes a tocopherol-free form of vitamin E Isomers, a blend of gamma and delta-tocotrienols, which have unique health and healthy aging benefits, and a unique blend of vitamin K1 with various forms of vitamin K2. It also includes a natural form of folate that addresses common genetic polymorphisms, and an effective dose of vitamin B12 to help overcome various malabsorption syndromes.

Comparison of Twice Daily Multi™, estimated Paleolithic diets, average US intakes and US RDA/AI

Table 1 (see link on back) compares the ingredients in TDM to estimated dietary intakes of the corresponding nutrients during the Paleolithic era, the current US RDA/AI, and average US intakes (based on data from NHANES 2001-2002).⁴⁰ The estimated Paleo era nutrient intakes are based on values reported by Cordain,⁶ a recalculation of Cordain's data with more advanced nutrition analysis software, and the evaluation of another sample Paleo diet.¹⁷⁻¹⁹ The data in Table 1 show that average Paleo nutrient intakes are significantly higher than current US RDA/AI, except for molybdenum. A two-capsule serving of TDM offers comparable amounts of essential micronutrients to those found in a 2000 kcal "Paleo-like" diet, with some adjustments based on average US intakes, nutrient bioavailability, and upper tolerable levels.

Magnesium, calcium, iron and copper are not included in TDM because this formula is designed to allow for more flexible and individualized supplementation of these nutrients. They may be derived from the diet or from condition-specific formulas such as OsteoForce™/OsteoForce™ Supreme, Osteoben® or various mineral formulas. Healthcare practitioners may recommend additional supplements based on patients' diets, lifestyle factors and clinical evaluations.

Comparison of Twice Daily Multi™ with other multivitamin/multimineral formulas

The majority of commercially available multivitamin and mineral formulas are designed to meet 100% of the RDA or AI, or some percentage thereof. These levels represent the minimum intake required to reduce risk for overt debility, manifested by deficiency diseases such as scurvy or pellagra; they were not derived for the purpose of optimizing health and physiological function, nor reducing risk for age- or lifestyle-related degenerative diseases.¹

Supplement Facts

Serving Size 2 capsules
Servings Per Container 30

Amount Per Serving	% Daily Value	Amount Per Serving	% Daily Value
Vitamin A (from Palmitate and Mixed Carotenoids)	960 mcg RAE 107%	Pantothenic Acid (as d-Calcium Pantothenate)	12 mg 240%
Vitamin C (as Ascorbic Acid)	500 mg 556%	Iodine (as Potassium Iodide)	150 mcg 100%
Vitamin D (as Cholecalciferol)	25 mcg (1000 IU) 125%	Zinc (as Zinc Bisglycinate Chelate)	15 mg 136%
Vitamin K (as K1 Phytanadiene, Vitamin K2 Menaquinone-4 and MenaQ7® Full Spectrum MK-6, MK-7, MK-9)	120 mcg 100%	Selenium (as Selenium Glycinate Complex)	200 mcg 364%
Thiamin (Vitamin B-1)(as Thiamin HCl)	2.3 mg 192%	Manganese (as TRAACS® Manganese Bisglycinate Chelate)	1 mg 43%
Riboflavin (Vitamin B-2)	2.8 mg 215%	Chromium (as TRAACS® Chromium Nicotinate Glycinate Chelate)	200 mcg 571%
Niacin (as Niacinamide and Niacin)	50 mg NE 313%	Molybdenum (as TRAACS® Molybdenum Glycinate Chelate)	100 mcg 222%
Vitamin B-6 (as Pyridoxal-5-Phosphate)	5.2 mg 306%	Vitamin E Isomers (as DeltaGold® delta and gamma tocotrienols)	15 mg *
Folate (as Quatrefolic® [6S]-5-methyltetrahydrofolate, glucosamine salt 800 mcg)	680 mcg DFE 170%	Boron (as Bororganic Glycine)	2 mg *
Vitamin B-12 (as Methylcobalamin)	500 mcg 20833%		
Biotin (as d-Biotin)	30 mcg 100%		

Other Ingredients: Cellulose (capsule), microcrystalline cellulose, vegetable stearate, silicon dioxide.

The optimal intake of vitamins and minerals for the general population remains open for debate and is a topic of ongoing research. For example, since 2001, research by Fenech et al. has investigated the potential to redefine the Australian RDAs for folate, B12, and other micronutrients to levels proven to support healthy DNA replication (also referred to as genomic stability), an important determinant of cellular health.¹²⁻¹⁵ Interestingly, the newly proposed Australian RDAs are higher than US RDAs for B12 (7 mcg versus 2.6 mcg) and folate (700 mcg versus 400 mcg), as are the estimated Paleolithic era intakes (see Table 1). This is likely not a coincidence since folate and B12 are necessary for adequate DNA replication, which is in turn critical to successful human evolution.¹⁶

Other multivitamin and mineral formulas contain ingredients at levels 10-100 times higher than the RDA/AI, based on potential to alleviate genetic polymorphisms affecting nutrient status² or to compensate for nutrient depletions resulting from commonly used pharmaceutical drugs. However, with the availability of clinical markers of nutritional deficiencies and genetics-based tests and recommendations, it is no longer necessary to provide such high levels of B vitamins in foundational formulas. Rather, additional nutrients can be supplemented based on relevant tests such as GenomicInsight™ Genomic Health Profile (offered by Diagnostic Solutions). Unlike other DNA tests, GenomicInsight™ enables clinicians to customize reports using the most advanced artificial intelligence, which integrates findings from peer-reviewed research. For example, the levels of vitamins B2, B6, B12 and folate found in TDM are adequate in maintaining healthy homocysteine (Hcy) levels for some individuals but not for those with single nucleotide polymorphisms on particular Hcy metabolic pathways and/or folate receptor activity.²⁰⁻²² The GenomicInsight™ report identifies which of these nutrients are required in higher doses in order to normalize Hcy levels. Other nutritionally relevant tests include NutrEval® (offered by Genova Diagnostics) and ALCAT Functional Cellular Assays (By Cell Science Systems).

The Guiding Principle of Evolutionary Biology

Human physiology was shaped by the type of diet naturally available for millions of years.³⁻⁶ Many researchers believe that optimal health may be best supported by the types and amounts of nutrients humans were exposed to during the Paleolithic era. A large body of research describes common characteristics of “Paleo-like” diets with respect to macro- and micronutrient content.^{6,10,11} Although precise intakes of plant and animal foods, and thus the exact composition of the human diet, may have differed based on season and geographic location, there are overarching general principles that can inform what the human body may be optimally suited to.

Evolutionary biology and cellular studies converge in a new approach for defining optimal intakes of nutrients essential to health and physiological function. This approach provides a rational framework for integrating findings from diverse but overlapping sciences: nutrition, biochemistry, physiology, paleontology and genetics.⁷⁻⁹ This is the foundation for optimizing diet and supplementation plans; beyond this, it is reasonable to make adjustments based on health, clinical status, age, genetics, performance needs and other goals.

Ingredient Highlights

Vitamin E Isomers: provided as DeltaGold®, an annatto-sourced tocopherol-free blend of gamma- and delta-tocotrienols. Tocotrienols have higher antioxidant activity and unique benefits not observed with tocopherols. (See the tocotrienols white paper and Annatto-E™ tech sheet for an extensive discussion of tocotrienol research and the shortcomings of tocopherols.) Tocotrienols are not easily found in common diets and their assimilation is impaired by concurrent consumption of tocopherols. Thus, tocopherols are not included in Twice Daily Multi™; they can easily be obtained through the consumption of nuts, seeds, avocado, various vegetable oils and many animal foods. This also creates the opportunity to supplement at the same time with additional higher doses of tocotrienols from Annatto-E™ or Annatto-E™ Synergy, since their absorption would be impaired by tocopherols.

Vitamin K: provided as two naturally occurring forms—K1 and K2 (as MK-4 and MenaQ7® Full Spectrum as MK-6, MK-7, MK-9). The RDA for vitamin K1 was derived solely based on optimizing blood clotting, but new research shows that higher levels are required to support the roles of vitamins K1 and K2 in bone metabolism, arterial health and more. The precise forms and specific levels of K2 characteristic of a Paleo diet are not known for certain but MK-4 was likely an important component since it is the main form stored in animal foods and in the human body. Consider using Tri-K™ for older men and women, especially postmenopausal women, who may need higher levels of vitamin K. (See the Tri-K™ tech sheet and the vitamin K chapter in the Textbook of Natural Medicine.)¹⁹

Folate: provided as Quatrefolic®, a glucosamine salt 5-MTHF form of folate shown to dissociate easily before absorption and raise plasma folate levels.²⁴ This form of 5-MTHF is likely more bioavailable than naturally occurring folates because they are covalently bonded to polyglutamate chains.²⁴ Folic acid is no longer considered an adequate source of folate for the following reasons: (a) genetic polymorphisms of folate metabolism are common and are responsible for a 35-70% reduced conversion of folic acid to the biological active form, 5-MTHF;^{24,25} (b) synthetic folic acid (derived from fortified foods, or supplements) may increase the risk of various cancers, reduce natural killer (NK) cell activity, and may have other detrimental effects;^{25,26} (c) human physiology is adapted to natural folates. Folic acid is not a naturally occurring molecule and has a distinct pathway of cell entry and different metabolic transformations compared to natural folates. These differences may be responsible for the detrimental effects associated with folic acid.^{25,27}

Vitamin B6: provided in the naturally occurring phosphorylated form, pyridoxal-5-phosphate.

Vitamin B12: provided in the naturally occurring methylcobalamin form. (See the Tricobalamin™ tech sheet for a detailed description of cobalamin metabolism, bioavailability issues and rationale for dosing at levels above the RDA in various populations.)

Niacin: included in two forms, as niacin and niacinamide; both occur naturally in foods.

Vitamin C: provided as ascorbic acid, at higher levels than in most multivitamins because average consumption of vitamin C from food in the US (94 mg) is well below evolutionary intakes (approx. 541 mg), due to diets deficient in fresh fruits and vegetables (see Table 1). It is an antioxidant and essential for optimal immune response, collagen biosynthesis, catecholamine metabolism, and dietary iron absorption.²³ In turn, poor collagen renewal results in impaired integrity of the skin, mucous membranes, blood vessels, and bone.²³ The RDA for vitamin C prevents only the extreme deficiency that results in scurvy; it does not provide for optimal health.²³

Vitamin A: 77% of the vitamin A in this formula is represented by a natural carotenoid mix from palm oil with the remainder as pre-formed vitamin A, retinyl palmitate for a total of 960 mcg RAE. This is based on the fact that the majority of vitamin A sources in the Paleolithic diet were derived from plant-sourced carotenoids rather than pre-formed vitamin A.⁶ Ideally, most vitamin A should be derived from a diet high in vegetables and fruits that provide carotenoids with vitamin A activity.

Mineral chelates: Zinc, manganese, molybdenum, chromium and boron are provided as highly bioavailable chelates. Mineral chelates do not depend on stomach acid for liberation and may be more effective for those with hypochlorhydria or other conditions that impair mineral absorption. Chelated minerals are designed to bypass obstacles to absorption and assimilation, such as food phytates, oxalates, fiber, ionic minerals or even medications that interfere with mineral absorption. Chelates are better tolerated and absorbed and are less likely to cause loose stools or other gastrointestinal discomfort.²⁸

Zinc: This mineral is involved in a multitude of basic biochemical functions. Zinc deficiency is known to have adverse clinical impacts on the epidermal, gastrointestinal, immune, skeletal, reproductive and central nervous systems.²⁹

Chromium: a trace mineral involved in maintaining healthy blood sugar levels and proper carbohydrate and fat metabolism.^{30,31} “Insufficient dietary intake of chromium leads to signs and symptoms that are similar to those observed for diabetes and cardiovascular diseases. Supplemental chromium given to people with impaired glucose tolerance or diabetes leads to improved blood glucose, insulin, and lipid variables.”³⁰

Vitamin D: The amount included in TDM is intended to be augmented by endogenously synthesized vitamin D from sun exposure and/or supplementation using one of Designs for Health’s vitamin D+K formulas, as guided by blood levels.

Iodine and Selenium: essential trace minerals for thyroid hormone synthesis and conversion.^{32,33}

Boron: There is no RDA for boron but this mineral appears to be important for various aspects of physiology. Research in humans and higher order animals support boron as “a bioactive beneficial element” that plays a role in bone health, brain function and immune response.^{34,35}

Biotin: There is no RDA for biotin but it is involved in several critical metabolic pathways, including “gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Biotin might regulate chromatin structures, gene expression, and DNA repair. Animal and human data suggest that poor biotin status adversely affects plasma lipid levels and can cause alopecia or erythematous dermatitis.”³⁶

Table 1: Twice Daily Multi™ ingredients compared to Paleo levels, RDA/AI and average intakes in US

Twice Daily Multi™ Ingredients Serving size: 2 capsules	Amt / 2 caps serving	Unit	Paleo Diet [range] (2000 Kcal) (ref. 6,17,18)	RDA M/F (ref. 1)	AI, M/F (ref. 1)	Average and range of US Intake
Vitamin A (from palmitate & mixed carotenoids from Palm Tree fruit), as follows:	960	mcg RAE		900 / 700		
Vitamin A (Mixed Carotenoids)	1700	IU	22548 [1941-57412]			10,521*
Vitamin A (Retinyl Palmitate)	1500	IU	1712 [143-3440]			1,406*
Vitamin C (as Ascorbic Acid)	500	mg	541 [345-748]	90 / 75		94.4 [24-238]*
Vitamin D (as Cholecalciferol [25 mcg])	1000	IU	469 [20-1540]	-	600-800	[204-288]*
Vitamin K (from K1 and K2), as follows:	120	mcg		ND	ND	
Vitamin K1 (Phytonadione)	90	mcg	716 [409-1000]	-	120 / 90	92.2 [30-222]*(US) 211.7 [9-991]**(EU)
Vitamin K2: MK-4, MK-6,7,9, as follows:	30	mcg	ND	ND	ND	29.1 [0.9-128]**
Vitamin K2: MK-4	10	mcg	ND	ND	ND	7.1 [0.5-28.2]**
Vitamin K2: MK-6, 7, 9 (as MenaQ7® Full Spectrum)	20	mcg	ND	ND	ND	21.4 [0-118.4]**
Vitamin B1 (as Thiamin HCl)	2.3	mg	2 [1.2-3.4]	1.2 / 1.1		1.6 [0.8- 3.4]*
Vitamin B-2, Riboflavin	2.8	mg	3 [2.4-4.2]	1.3/ 1.1		2.2 [1.02-4.14]*
Vitamin B-3 (as Niacinamide, Niacin)	50	mg NE	51 [30-66]	16 / 14		22.8 [10.8-41.9]*
Vitamin B5 (as d-Calcium Pantothenate)	12	mg	11 [9-13]	5 / 5		6 (ref.42)
Vitamin B-6 (as Pyridoxal-5-Phosphate)	5.2	mg	5.2 [2.9-6.7]	1.7 / 1.5		3.7 [0.8-3.7]*
Folate (as Quatrefolic® [6S]-5-methyltetrahydrofolate, glucosamine salt) (DFE=dietary folate equivalents)	680	mcg DFE	810 [527-1034]	400		559 [251-1126]*
Vitamin B-12 (as Methylcobalamin)	500	mcg	15 [7-29]	2.4 / 2.4 or 500		5.4 [1.73-12.6]*
Biotin (as d-Biotin)	30	mcg	31 [43-52]	30		[35-70] (ref 43)
Zinc (as Zinc Bisglycinate Chelate)	15	mg	21 [11-32]	11 / 8		12.9 [5.4-22.3]*
Selenium (as Selenium Glycinate Complex)	200	mcg	202 [108-277]	55 / 55		113 [52-195]*
Manganese (as TRAACS® Manganese Bisglycinate Chelate)	1	mg	4.4 [2.8-6.1]	2.3 / 1.8		[2.1-2.2](F), [2.6-2.8](M) (ref.38)
Chromium (as TRAACS® Chromium Nicotinate Glycinate Chelate)	200	mcg	32 [3-61]	35 / 25		[39-54](M), [23-29](F) (ref. 1)
Iodine (as Potassium Iodide)	150	mcg	40 [21-57]	150 /150		[138-353] (ref. 41)
Molybdenum (as TRAACS® Molybdenum Glycinate Chelate)	100	mcg	34	45 / 45		180 [120-400]*
Boron (as Bororganic Glycine)	2	mg	1.8 [1-2.5]	ND	ND	1 [0.4-2.4]*
Vitamin E isomers (as DeltaGold® delta and gamma tocotrienols)	15	mg	ND	ND	ND	2 (ref. 37)

* NHANES 2001-2002 (ref. 40); ** (ref.19); ND = No data available

Recommended Use:

- Take two capsules per day with meals, or as directed by your health care practitioner.

Complementary formulas: For individualizing supplementation, consider combining Twice Daily Multi™ with the following DFH formulations:

- OsteoForce™, OsteoForce™ Supreme, Osteoben®, or any DFH calcium and/or magnesium products as indicated based on diet, sex, age, and health status
- PaleoGreens®, PaleoReds®, EssentiaGreens™, or other antioxidant formulas based on diet and oxidative stress status
- For additional B12 and/or folate: Tricobalamin™, Trifolamin™, L-5-MTHF (0.5mg, 1mg, 5mg)
- Ferrochel™ for additional iron

For a list of references cited in this document, please visit:


<https://www.designsforhealth.com/techsheet-references/twice-daily-multi-references.pdf>

Dosing recommendations are given for typical use based on an average 150 pound healthy adult. Healthcare practitioners are encouraged to use clinical judgement with case-specific dosing based on intended goals, subject body weight, medical history, and concomitant medication and supplement usage.

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To contact Designs for Health, please call us at (860) 623-6314, or visit us on the web at www.designsforhealth.com.

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