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Food Supplementation with Vitamins and Minerals: An Overview

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Abstract

Vitamins are organic substances that are essential for normal metabolism, growth, development, and regulation of cell function. Mineral elements are non-organic substances. They constitute 4% of the body mass. Multivitamins and minerals are commonly used as dietary supplements to maintain good health and prevent chronic diseases. In this chapter, we described selected vitamins and minerals used as nutritional supplements. We presented their dietary sources as well as their absorption, metabolism, storage and functions in human body. We also discussed their benefits and potential harmful effects associated with deficiency or excess intake. The prevalence, recommended intakes, regulatory status and health effects of supplementation with these micronutrients were also detailed. Finally, the use of vitamins and minerals as food additives was described in this chapter.

Keywords: vitamins, minerals, dietary sources, bioavailability, recommended intakes

1. Introduction

According to the US Food and Drug Administration (FDA), a dietary supplement is a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet [1]. The use of dietary supplements is widespread in the United States, Canada as well as in several European countries [2–5]. Up to 50% of adults and one-third of children in economically advanced economies consume these supplements [6]. Dietary supplements may be used to correct deficiencies or maintain adequate intake of some nutrients. However, they may be harmful with excess intake. Hence, it is necessary to control their levels for a safe intake [7–9]. Vitamins and minerals are the most frequently used dietary supplements among adults in United States [10]. Thirteen vitamins (A, B₁, B₂, B₃, B₅, B₆, B₈, B₉, B₁₂, C, D, E, K) and fifteen minerals (calcium, phosphorus, potassium, sodium, chloride, magnesium, iron, zinc, iodine, chromium, copper, fluoride, molybdenum, manganese, and selenium) have been recognized as essential for the maintenance of human health [11]. The first multivitamin/mineral (MVM) formulas were introduced in the 1930s and the most common definition of this term is a dietary supplement containing 3 or more vitamins and minerals [12]. MVM supplements are recommended to prevent or treat nutrition-related infectious diseases such as the Acquired Immune Deficiency Syndrome (AIDS) disease that arises from human immunodeficiency virus (HIV) infection and which is responsible for more than half of total deaths in

some developing countries [13]. Tuberculosis is another chronic infectious disease that is correlated to the presence of vitamin A levels in human bodies. Indeed several epidemiological studies found that healthy population has significantly higher vitamin A serum levels than tuberculosis patients [14, 15]. MVM supplements are also widely used to promote health and prevent chronic diseases and cancer. However, controversial findings were reported on the beneficial effect of these supplements on cardiovascular diseases prevention [16–18]. The aim of this chapter was to give a global idea on the main vitamins and minerals that are essential in our life and to present the most important users of MVM supplements as well as their frequency of use and the related deficiency diseases.

2. Vitamins

Vitamins are organic molecules that are necessary for the organism and which humans cannot synthesize in a sufficient quantity. Unlike habitual nutrients that are introduced in large quantities in the body and that contribute to the production of energy, only small amounts of vitamins are required for a healthy metabolism (micrograms or milligrams per day). Vitamins are obtained naturally from a balanced and diversified diet or can be added to foods. Their deficiency can cause health disorders such as cardiovascular diseases or cancers while an overconsumption can lead to toxic effects in the medium or long term (**Table 1**) [1–5].

Vitamin	Deficiency symptoms	Excess intake symptoms
Vitamin A	<ul style="list-style-type: none"> • Measles • Night blindness • Respiratory infection • Diarrhea • <i>Xerophthalmia</i> disease 	<ul style="list-style-type: none"> • Nausea and vomiting • Anorexia • Abdominal pain • Skin desquamation • Blurred vision
Vitamin B ₁	<ul style="list-style-type: none"> • Anorexia and muscle weakness • Gastrointestinal disturbances • Peripheral and central neuropathy • Cardiovascular irregularities • <i>Beriberi</i> disease 	<ul style="list-style-type: none"> • Gastric upset
Vitamin B ₂	<ul style="list-style-type: none"> • Angular stomatitis and glossitis • Seborrheic dermatitis • Intense photophobia • Superficial vascularization of the cornea 	<ul style="list-style-type: none"> • No toxic effects
Vitamin B ₃	<ul style="list-style-type: none"> • Fatigue and headache • Diarrhea • Dementia and dermatitis • Pigmented rash • <i>Pellagra</i> disease 	<ul style="list-style-type: none"> • Flushing of the skin • Hyperuricemia • Hepatic and ocular abnormalities • Hyperglycemia • Liver damage
Vitamin B ₆	<ul style="list-style-type: none"> • Epileptiform convulsions • Stomatitis and cheilitis • Glossitis • Irritability • Depression and confusion 	<ul style="list-style-type: none"> • No toxic effects

Vitamin	Deficiency symptoms	Excess intake symptoms
Vitamin B ₉	<ul style="list-style-type: none"> • Irritability and hostility • Memory loss and paranoid behavior • Poor growth • Glossitis • Megaloblastic anemia 	<ul style="list-style-type: none"> • No toxic effects
Vitamin B ₁₂	<ul style="list-style-type: none"> • Weakness and fatigue • Shortness of breath and palpitations • Memory loss and dementia • Loss of appetite • Flatulence and constipation 	<ul style="list-style-type: none"> • No toxic effects
Vitamin C	<ul style="list-style-type: none"> • Fatigue • Ecchymoses and coiled hairs • Myocardial infarctions • Stroke • Scurvy disease 	<ul style="list-style-type: none"> • Diarrhea • Nausea • Kidney stones • Iron overabsorption • Gastrointestinal disturbances
Vitamin D	<ul style="list-style-type: none"> • Bow legs or knock knees • Pelvic and thoracic deformities • Spine curvature • Epiphyseal abnormalities • Rickets and Osteomalacia diseases 	<ul style="list-style-type: none"> • Nausea and vomiting • Hypercalcaemia and muscle weakness • Polyuria and polydipsia • Hypercalciuria • Anorexia and thirst

Table 1.
 Deficiency and toxic effects of selected vitamins.

Thirteen vitamins were discovered during the first half of the twentieth century and the last discovery was that of vitamin B₁₂ in 1948. These compounds have diverse biochemical functions such as antioxidants, coenzymes, hormones or mediators of cell signaling. They are classified in two categories: fat-soluble (e.g. vitamins A and D) and water-soluble (e.g. vitamins B and C). While water-soluble vitamins should be consumed daily, fat-soluble vitamins can be consumed at less regular intervals due to their ability to be stored in the liver and in adipose tissue [1, 2, 6]. Among the thirteen known vitamins, six water-soluble and three fat-soluble ones were described, due to their high nutritive value and their frequent use as food supplements and nutritional additives.

2.1 Vitamin A

Vitamin A is a fat-soluble vitamin discovered in the early 1900s by McCollum and independently by Osborne and Mendel as an essential dietary factor for growth [2, 7]. Forms of vitamin A include provitamin A carotenoids (principally β -carotene, α -carotene, and β -cryptoxanthin), retinol (preformed vitamin A), retinal, retinoic acid and retinyl esters. The requirements for vitamin A are expressed in retinol activity equivalents (RAEs), such that 1 μ g RAE = 1 μ g preformed retinol = 12 μ g β -carotene = 24 μ g α -carotene or β -cryptoxanthin [8, 9].

2.1.1 Dietary sources

Preformed vitamin A is found naturally only in animal-based products such as liver and fish liver oil, dairy products, eggs and fish. It is also used in food

fortification of sugar, cereals, fats or condiments. The main dietary sources of provitamin A carotenoids are pigmented vegetables and fruits including spinach, parsley, amaranth, lettuce, carrot, papaya, mango, etc. [1, 9, 10].

2.1.2 Absorption, metabolism and storage

About 70-90% of preformed vitamin A is absorbed from the small intestine dissolved in lipid micelles. Carotenoids are absorbed into the small intestine by passive diffusion. Their biological availability varies between 5 and 60% [8].

After absorption, retinal esters and nonhydrolyzed carotenoids are transported to the liver in chylomicrons and chylomicron remnants. About 90% of retinol is stored in the liver as retinol palmitate. The remaining fraction is transported to other adipose tissues by Retinol Binding Protein (RBP). The total body vitamin A is excreted in the urine or the feces and to a lesser extent in the bile [1, 9, 11].

2.1.3 Function

Vitamin A is required for normal vision, embryonic development, reproduction, gene expression, growth and immune function [7, 9]. In the visual system, the dim-light vision is related to the presence of rhodopsin, a photosensitive pigment formed in rod cells, after the binding of the 11-*cis*-retinaldehyde to the optin protein. Following an equivalent mechanism, the vision of shapes and colors is carried out in the presence of iodopsin pigments formed in the cones after the binding of the 11-*cis*-retinaldehyde to the photopsin protein [4, 10, 11]. As regards embryonic development, retinoic acid as well as endogenous retinoids play an important role in the anterior-posterior development of the central body axis and in limb development. Their concentrations are highly regulated, both spatially and temporally [3]. Vitamin A is essential for reproduction too, through the biosynthesis of glycoproteins specific to spermatogenesis [4, 11]. It is also required to regulate the expression of a number of genes through interactions of retinoic acid with various cytosolic and nuclear receptors [11, 12]. These genes include the growth hormone gene, and therefore the normal growth and development of children are affected by vitamin A deficiency. Finally, vitamin A enhances cellular and humoral immunity through all-trans-retinoic acid. It stimulates the synthesis of immunoglobulins and the proliferation of lymphocytes and thymocytes [4, 11].

2.2 Vitamin B₁ (thiamin)

Historically, vitamin B₁ has been known as the preventive and curative agent of the human disease “beriberi” [2, 7]. Its structure determination and synthesis were carried out in 1936. This water-soluble vitamin includes substituted pyrimidine and thiazole moieties linked by a methylene bridge. Three phosphorylated forms of thiamin occur in nature: thiamin monophosphate, thiamin diphosphate (the active coenzyme also known as thiamin pyrophosphate) and thiamin triphosphate. Thiamin is particularly sensitive to sulfites and polyphenols, which destroy its biological activity [8].

2.2.1 Dietary sources

The most abundant *sources* of vitamin B₁ include yeast and yeast extract, whole cereal grains, nuts, lean pork, wheat bran, heart, kidney, liver and fortified food such as bread and breakfast cereals. Fresh food, such as fruits, vegetables and dairy

products except butter, could protect against vitamin B₁ deficiency if it is consumed regularly and in sufficient amount [1, 3, 7].

2.2.2 Absorption, metabolism and storage

Dietary thiamin phosphates are hydrolyzed to free thiamin by intestinal phosphatases. Then, absorption of free thiamin takes place in the duodenum and proximal jejunum [3, 4]. Two parallel mechanisms are involved in thiamin absorption: a saturable active transport at low physiological concentrations of the vitamin and a passive diffusion at higher concentrations [3, 7, 9]. Transport of thiamin is modulated by various biological factors such as age, diabetic state and alcohol exposure [7]. Some thiamin is phosphorylated to thiamin monophosphate in the intestinal mucosa and both free thiamin and thiamin monophosphate circulate in the bloodstream, the former bound to plasma proteins. Approximately 30 mg of total thiamin is found in human body, of which about 80% is thiamin diphosphate, 10% is thiamin triphosphate, and the remainder is free thiamin and thiamin monophosphate. Due to the low storage capacity and the relatively high turnover rate of thiamin, a regular intake of this vitamin is then necessary [1, 3].

2.2.3 Function

Thiamin diphosphate is a coenzyme for three multienzyme complexes involved in the oxidative decarboxylation of oxoacids: pyruvate dehydrogenase, α -ketoglutarate dehydrogenase and branched-chain ketoacid dehydrogenase. Thiamin triphosphate plays a role in nerve transmission for sodium and potassium transport [1, 3].

2.3 Vitamin B₂ (riboflavin)

The water-soluble vitamin riboflavin was synthesized independently by Kuhn's and Karrer's groups in 1935 [3]. This fluorescent, yellow crystalline compound was discovered during the 1920s as a preventive factor from human "pellagra" as well as "beriberi" disease. Riboflavin is a flavin with the flavin ring attached to an alcohol related to ribose [2]. It is a relatively heat-stable molecule but it is rapidly inactivated in ultraviolet (UV) light [7].

2.3.1 Dietary sources

Major food sources of vitamin B₂ include milk and dairy products as well as meat and meat products. Green vegetables such as collard greens, turnip greens and broccoli are good sources of riboflavin. Natural grain products contain low amounts of riboflavin but enrichment of these food items with the vitamin has improved its intake. Vitamin B₂ is also widely used as food color due to its intense yellow color [2, 3, 7].

2.3.2 Absorption, metabolism and storage

Flavin coenzymes are hydrolyzed by alkaline phosphatase in the upper small intestine to free riboflavin, which is then absorbed. Absorption is enhanced when riboflavin is ingested along with other foods and in the presence of bile salts. Much of the absorbed riboflavin is phosphorylated in the intestinal mucosa and enters the bloodstream as riboflavin phosphate. About 50% of plasma riboflavin in plasma is free riboflavin, with somewhat less flavin adenine dinucleotide (FAD) and less

than 10% flavin mononucleotide (FMN). The average concentration of riboflavin in plasma is about 0.03 μM [3, 4, 7]. The liver is the main storage organ of vitamin B₂. Other storage sites are the spleen, kidney and cardiac muscle. Urinary excretion of vitamin B₂ occurs predominantly in the form of free riboflavin with a small amount as a variety of its glycosides and metabolites [4].

2.3.3 Function

Riboflavin functions as the precursor of the flavin coenzymes, FMN and FAD, and of covalently bound flavins. These coenzymes catalyze numerous oxidation–reduction reactions in several metabolic pathways including the mitochondrial electron transport chain. The majority of flavoproteins require FAD as the prosthetic group rather than FMN. Other major functions of riboflavin include drug, lipid and steroid metabolisms [3, 7, 8].

2.4 Vitamin B₃ (niacin)

Niacin is a generic term referring to two vitamers nicotinic acid and nicotinamide. Nicotinic acid was discovered by Huber in 1867 as a product of nicotine oxidation, but its curative and preventive role against “pellagra” disease was not recognized until much later, in 1938. Niacin is a whitish water-soluble crystalline compound. It can be synthesized in the body from the essential amino acid tryptophan, which constitutes an important route for meeting the body’s niacin requirement [1, 2, 7].

2.4.1 Dietary sources

Niacin requirements are generally expressed as mg niacin equivalents; 1 mg niacin equivalent = 1 mg preformed niacin + $1/60 \times$ mg tryptophan. Due to the contribution of tryptophan, foods rich in proteins are important sources of the vitamin. Lean red meat, fish, liver and poultry contain high amounts of both niacin and tryptophan. Other contributors to niacin intake include ready-to-eat cereals supplemented with nicotinic acid. Vegetables and fruits provide useful amounts of the vitamin, depending upon the dietary intake [1, 3, 7].

2.4.2 Absorption, metabolism and storage

Niacin is present in food largely in the form of the nicotinamide nucleotides, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These nucleotides are hydrolyzed to free nicotinamide in the intestinal lumen. At low concentrations, absorption from the small intestine is mediated by a sodium-dependent facilitated diffusion. At higher amounts, absorption is by passive diffusion [7, 9]. Niacin compounds entering the portal circulation are either transported to the liver or internalized by erythrocytes. In the liver, nicotinic acid and nicotinamide, together with tryptophan, are converted to (NAD). On reaching the tissues, the niacin vitamers are used for the intracellular synthesis of NAD and NADP. The liver plays an important role in the preparation of niacin for urinary excretion, converting excess niacin to methylated derivatives [3, 7].

2.4.3 Function

The nicotinamide nucleotides NAD and NADP play a major role in a wide variety of oxidation–reduction reactions. The NAD coenzyme is involved in catabolic

reactions while NADP is more often required in synthetic mechanisms such as the synthesis of steroids and fatty acids [1]. The coenzyme NAD is easily convertible to NADP and vice versa, while both molecules can also exchange their oxidation state. This conversion maintains a balance between the energy-consuming synthetic reactions and the catabolic reactions that produce energy [1].

2.5 Vitamin B₆

The pure crystalline water-soluble vitamin B₆ was first isolated in 1938 by Lepkovsky, then synthesized by Harris and Folkers in 1939. There are six nutritionally active B₆ vitamers, namely pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM), and the corresponding 5'-phosphate esters pyridoxine phosphate (PNP), pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP) [2, 3]. Aqueous vitamin B₆ solutions are colorless, except for PLP solutions, which are yellow and not very stable in neutral or alkaline medium [11].

2.5.1 Dietary sources

High quantities of vitamin B₆ are found in yeast, liver, fortified cereals and grain germs. Other important sources include nuts, pulses, meat, fish, avocado, banana and potatoes. Eggs, fruit and milk, contain relatively low concentrations of the vitamin [1, 3, 9].

2.5.2 Absorption, metabolism and storage

The absorption of vitamin B₆ occurs following the hydrolysis of the phosphorylated forms in the lumen of intestine through a sodium-dependent carrier-mediated system [7]. Once absorbed, the different forms of the vitamin B₆ vitamers are interconverted and conveyed to the liver in the form of free non-phosphorylated vitamers. In the liver, the vitamers are accumulated by diffusion and converted to phosphorylated forms, under the action of pyridoxal kinase enzyme. The PNP and PMP are oxidized to PLP by pyridoxine oxidase. A proportion of PLP is released into the bloodstream bound to plasma albumin. The remaining portion of PLP is dephosphorylated and oxidized to pyridoxic acid, which is released into the plasma and excreted in the urine [3].

2.5.3 Function

The metabolically active vitamer is PLP, which is involved in a wide variety of amino acids reactions, including transamination, transulphuration, desulphuration and decarboxylation. PLP is also required in the regulation of steroid hormone actions. In addition, PLP vitamer acts as the cofactor of glycogen phosphorylase in muscle and liver and has an essential role in lipid metabolism and immune function [3, 4, 8].

2.6 Vitamin B₉ (folates)

The water-soluble vitamin B₉ is represented by the group of folates (from *folium* the Latin word for leaf). The isolation, chemical structure determination and synthesis of vitamin B₉ was carried out in 1946 by Angier's group [3]. Since the early 1990s, the associations between folate intake and birth outcome or chronic disease risk were investigated. Research studies established a reduction in the risk of neural tube defects after a daily periconceptual supplementation with folic acid. These

important results led to the implementation of public health policies that include mandatory folic acid fortification in North America [7].

2.6.1 Dietary sources

Good sources of folate include fortified grain products, orange juice, fresh dark green leafy vegetables, lentils, kidney beans, lima beans, avocado, peas and peanut products. Meat in *general* is not a good source of folate, except liver [1, 3, 7].

2.6.2 Absorption, metabolism and storage

About 80% of dietary folate occurs in a polyglutamate form, which is hydrolyzed to the monoglutamate form before absorption by enterocytes primarily in the jejunum. Monoglutamyl folate is then transported across the intestinal mucosa via a saturable, pH dependent active transport process. Nevertheless, at high concentrations, the intestinal uptake takes place by a nonsaturable passive diffusion. Plasma folate, primarily 5-methyl THF, is distributed in two major forms: free folate and folate bound to albumin. A small proportion of plasma folate (less than 5%) is bound to high-affinity binders [3, 4, 8]. The majority of reduced monoglutamates arriving at the liver from the intestine is metabolized and retained or released into the blood or bile [3]. Folate is excreted in the urine as folate derivatives and only 1%-2% of the vitamin is emitted as intact urinary folate [7].

2.6.3 Function

Due to their chemical structure, folates play a major role in the mobilization of one-carbon units in intermediary metabolism. Such reactions are required in the synthesis of the purines guanine and adenine and the pyrimidine thymine, which are used in the formation of nucleoproteins deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) [2, 3]. Folates are also essential in the metabolism of amino acids, by means of THF derivatives that serve as donors of one-carbon units in a variety of synthetic reactions [3].

2.7 Vitamin B₁₂

Vitamin B₁₂ was discovered after a series of important contributions from different fields including medicine, chemistry and microbiology, which led to the awarding of Nobel Prizes. The chemical structure of vitamin B₁₂ was elucidated by the x-ray crystallographer Dorothy Hodgkin, that was awarded the Nobel Prize for chemistry in 1964. The total chemical synthesis of vitamin B₁₂ took 11 years and was led by Robert Woodward, who received the Nobel Prize in Chemistry in 1965 [7]. The term vitamin B₁₂ is used as a generic descriptor of cobalamins, which have a structure similar to heme but the central iron atom is replaced by a cobalt atom. Cyanocobalamin, a water-soluble purplish red powder, is the most stable of the vitamin B₁₂-active cobalamins. It is widely used in food supplementation and pharmaceutical preparations. However, it is a light sensitive molecule [3, 11].

2.7.1 Dietary sources

Vitamin B₁₂ is found almost exclusively in foods of animal origin and liver is the most abundant dietary source of the vitamin followed by kidney and heart [2, 3]. Other important sources include milk, fish, eggs, shellfish and muscle meat. Different forms of vitamin B₁₂ exist in foods such as adenosyl- and hydroxocobalamins in

meat and fish, Sulphitocobalamin in canned meats and fish and small quantities of Cyancobalamin in egg white and cheeses [3].

2.7.2 Absorption, metabolism and storage

Vitamin B₁₂ is absorbed by two different mechanisms: one active and the other passive. The major route of vitamin B₁₂ active absorption is by attachment in the intestinal lumen to a small glycoprotein secreted by the parietal cells of the gastric mucosa named intrinsic factor. In the stomach, vitamin B₁₂ binds to cobalophilin protein, which is hydrolyzed in the duodenum, releasing vitamin B₁₂ to bind to intrinsic factor. In plasma, vitamin B₁₂ circulates bound to transcobalamin I and II proteins, which prevent the vitamin from urine excretion as it passes through the kidney [3, 8]. With over 60% of the total vitamin content present in the body, the liver is the richest organ in vitamin B₁₂.

2.7.3 Function

Vitamin B₁₂ is involved in the metabolism of proteins, fats and carbohydrates. It is essential in the regeneration of the 5-methyl-folic acid into folic acid, which prevents from its direct urine excretion. In addition, vitamin B₁₂ contributes to the transport and storage of folic acid in cells and plays a crucial role in the synthesis of myelin lipoprotein [1]. Vitamin B₁₂ is also an important cofactor in the maintenance of normal DNA synthesis, the regeneration of methionine for adequate protein synthesis and methylation capacity, and the avoidance of homocysteine accumulation leading to various degenerative diseases [7].

2.8 Vitamin C (ascorbic acid)

The scurvy disease, due to vitamin C deficiency, was described in the Ebers papyrus of 1500 B.C. and by Hippocrates [4]. It was endemic in many areas, especially in the earliest explorations of the New World where over 2 million sailors died of scurvy during the era, often called the “Age of Sail” [7]. The structure of vitamin C, was elucidated in 1933 by Walter Haworth and his associates, at the University of Birmingham in England. It was synthesized in the same year by the same research team [3]. Vitamin C is the generic descriptor for all compounds with the biological activity of L-ascorbic acid. It is a water-soluble white crystalline powder, that is stable at solid state and that serves as a good reducing agent [2, 11].

2.8.1 Dietary sources

Vitamin C is synthesized by almost all living organisms, except humans and other primates, guinea pigs, fish, fruit-eating bats and some exotic birds [3, 8]. It occurs in significant amounts in green vegetables, fresh fruits, especially citrus fruits and blackcurrants and in animal organs such as liver, kidney and brain. Other good sources of vitamin C include potatoes, tomatoes, strawberries and cabbage. Muscle meat and cereal grains are poor dietary sources of the vitamin. Cooking causes significant losses of vitamin C through leaching into the cooking water and also atmospheric oxidation [3, 7].

2.8.2 Absorption, metabolism and storage

The biologically active forms of vitamin C are ascorbic acid and dehydroascorbic acid. Both vitamers are absorbed across the buccal mucosa by carrier-mediated

passive processes. At physiological intakes, the intestinal absorption of vitamin C is by active transport mechanism, while at high doses, there is a less efficient passive diffusion, which proceeds at a very low rate [11]. In plasma, vitamin C occurs mainly as free ascorbate, and dehydroascorbic acid is present at undetectable concentrations. Liver has the greatest store of vitamin C in the body by virtue of its size. Other organs containing ascorbate include kidney, pancreas and brain. Excretion of vitamin C is mainly in urines with negligible amounts of ascorbic acid or its catabolites excreted in feces [3].

2.8.3 Function

Vitamin C acts as a cofactor in various hydroxylation reactions catalyzed by oxygenases. For example, vitamin C plays an important role in collagen and catecholamines biosynthesis. It is also involved in carnitine synthesis, which takes place in liver from the amino acid lysine. Both vitamin C and copper act as cofactors in the catabolism of phenylalanine and tyrosine enzymes, which is impaired with vitamin C deficiency. In addition, some peptide hormones like peptidylglycine are activated in the presence of copper, oxygen and ascorbate. By promoting the incorporation of iron into ferritin, vitamin C influences the distribution of this mineral in the body. It is also required in the metabolism of histamine and nitrosamine. Moreover, vitamin C increases the mobility of leukocytes and protects their membranes from oxidative attacks. Due to its high reducing power, vitamin C has also an important biochemical function of antioxidant. The powerful antioxidant action of vitamin C allows it to protect the sperm from AND oxidative attacks or the eye from radical attacks [11].

2.9 Vitamin D

Rickets, a disease due to vitamin D deficiency, occurred in ancient times about 50,000 B.C. [7]. Due to air pollution and little sunlight, Rickets has spread in northern Europe, England, and the United States during the Industrial Revolution. There are two common forms of vitamin D: cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂). The structures of vitamin D₂ and vitamin D₃ were determined by Windaus and his associates respectively in 1932 and in 1936, in Germany. Dorothy Hodgkin, the Nobel laureate x-ray crystallographer, was the first to develop a three-dimensional model of vitamin D₃. While vitamin D₂ is synthesized in plants, fungi and yeasts by the solar irradiation of ergosterol, vitamin D₃ is produced *in vivo* by the action of sunlight on skin [3, 7].

2.9.1 Dietary sources

There are relatively few sources of vitamin D. The richest dietary sources are fish-liver oils, especially halibut-liver oil. Other major sources of the vitamin are fatty fish such as tuna, sardines, pilchards or herring. Eggs, mammalian liver and dairy products are good sources of vitamin D. However, vegetables, fruit and cereals are exempt of the vitamin. Fortified products include margarine, breakfast cereals and milk. Vitamin D can also be synthesized by the skin after exposure to sunlight. This endogenous synthesis constitutes a much more important source of vitamin D than foodstuff [2, 3, 8].

2.9.2 Absorption, metabolism and storage

Vitamin D is absorbed in lipid micelles and incorporated into chylomicrons through the lymphatic system. Following intestinal absorption, vitamin D is rapidly

taken up by the liver, where it is hydroxylated to form the 25-hydroxy derivative calcidiol before entering the circulation bound to a vitamin D binding globulin. On arrival at the kidney, the calcidiol undergoes 1-hydroxylation to yield the active metabolite 1,25-dihydroxyvitamin D (calcitriol) or 24-hydroxylation to yield an apparently inactive metabolite, 24,25-dihydroxyvitamin D (24-hydroxycalcidiol) [3, 8]. These conversions are regulated in response to the concentrations of calcium and phosphorous minerals in plasma. Vitamin D is mainly excreted in bile after catabolism into highly polar inactivation products by the liver [3].

2.9.3 Function

The primary physiologic role of vitamin D is to maintain the plasma concentrations of calcium and phosphorous in the body. Calcitriol acts to rise intestinal absorption of calcium, to decrease its excretion and to mobilize the mineral from bone [4]. It plays an important role in immune muscle functions, nervous system and cell differentiation. In addition, it regulates more than 50 genes by activating nuclear receptors that modulate gene expression. 24-hydroxycalcidiol has also a biological activity in cartilage or in bone formation during the development of knockout mice [4].

3. Minerals

Minerals are inorganic substances that are required for normal metabolism, development, growth, body structure, cell function regulation, and electrolyte

Mineral	Deficiency symptoms	Excess intake symptoms
Calcium	<ul style="list-style-type: none"> • Memory loss • Muscle cramps • Increased risk of fractures • Osteopenia • Osteoporosis 	<ul style="list-style-type: none"> • Hypercalcemia • Renal insufficiency • Kidney stones
Magnesium	<ul style="list-style-type: none"> • Ischemic heart disease • Hypertension • Osteoporosis • Diabetes • Stroke 	<ul style="list-style-type: none"> • Diarrhea • Muscular paralysis • Central nervous system depression
Iron	<ul style="list-style-type: none"> • Fatigue and weakness • Anemia • Mental retardation • Brain damage • Behavioral impairment 	<ul style="list-style-type: none"> • Vomiting and diarrhea • Liver, kidney and heart diseases • Neurological defects • Gastrointestinal effects • Hormonal abnormalities
Iodine	<ul style="list-style-type: none"> • Goiter and cretinism • Hypothyroidism • Growth retardation • Neurological defects • Reproductive disturbance 	<ul style="list-style-type: none"> • Goiter • Hypothyroidism • Hyperthyroidism • Thyroiditis

Table 2.
 Deficiency and toxic effects of selected minerals.

balance [13]. Minerals are divided in two groups, the major (macro) minerals, which are present in the human body in concentrations greater than 100 milligrams per kilogram and trace (micro) minerals occurring at much lower amounts (micrograms or milligrams per kilogram) [8]. Minerals are considered as essential when deficiency symptoms are noted with depletion or removal. Typically, calcium constitutes about 46% and phosphorous about 29% of total body minerals. Chloride, potassium, sulfur, sodium and magnesium together account for about 25%, while essential trace elements represent less than 0.3% of the total. Bone is the primary storage site for many essential elements (99% of the total calcium, 80 to 85% of phosphorous and some 70% of magnesium), while the thyroid gland contains more than 80% of the total body iodine. Generally, mineral distribution within the body's tissue is not uniform and each organ has a specific mineral composition [14]. **Table 2** shows the benefits and potential harmful effects associated with deficiency or excess intake of four frequently used minerals as food additives and/or supplements [1, 2, 9, 10, 15].

3.1 Calcium

Calcium is a soft, silvery white metal ranked fifth in order of abundance among the elements in the earth crust. It has an atomic weight of 40.08, and an atomic number of 20. Calcium is found in nature only in compounds, mainly as carbonate, fluoride, sulfate and phosphate [8, 14]. Metallic calcium or calcium compounds are used in steel industry, plastics, cement manufacture, paper industry, alloys production, etc. Calcium is the most abundant mineral in the organism and 99% of this macro mineral is found in bone and teeth [14].

3.1.1 Dietary sources

Dairy products are the most important dietary sources of calcium including milk, yoghurt and cheese. Tinned fish such as sardine, oilseeds like almonds and dried fruit are also good sources of calcium. Generally, foods of plant origin are poor sources of calcium. However, due to their high level of consumption they make a significant contribution to the total calcium intake. Contributions from calcium-enriched foods such as breakfast cereals and dietary supplements containing calcium salts may be also significant [8].

3.1.2 Absorption, metabolism and storage

The absorption of calcium takes place by two mechanisms. The first is active and regulated by vitamin D and the second is by passive diffusion. At low levels of dietary calcium, most of the absorption is by active transport and is done principally in the duodenum. Passive diffusion is more important at high calcium intakes and ileum is the most active absorptive site. The large intestine contributes also to calcium absorption. Generally, only 30 to 50% of dietary calcium is normally absorbed [14]. Calcium absorption is largely dependent on other nutrients in the diet, hormonal status and physiological conditions such as pregnancy and breastfeeding [1]. Lactose and vitamin C supplementation increase calcium absorption. Dietary sources rich in oxalic acid or phytic acid could inhibit calcium absorption from foodstuff [9]. Calcium homeostasis is regulated by calcitonin and parathyroid hormones that are associated to the active form of vitamin D, 1,25-dihydroxyvitamin D. Bone is the primary storage site of calcium and the decrease of calcium levels in blood leads to a quick metal mobilization from the bone to bring the blood levels back to normal. Plasma contains from 9 to 12 mg of calcium per 100 mL, which

is distributed in ionized, protein bound and complexed fractions. Excretion of calcium is done principally in feces.

3.1.3 Function

The primary role of calcium in the body is to form the structures of bone and teeth. During skeletal growth and maturation, calcium accumulates in the skeleton at an average rate of 150 mg/day. During maturity, the skeleton is in calcium equilibrium until the age of fifty, from which the bone is lost from all skeletal sites. This bone loss increases the risk of hip fracture with aging. Extraskkeletal calcium, which represent around 1% of the total body calcium, play important roles in various essential functions in body metabolism such as enzymatic activation, cell division, muscular contraction, nerve transmission and vesicular secretion [1, 8].

3.2 Magnesium

Magnesium is a silvery white metal ranked seventh in order of abundance in the crust. It has an atomic number of 12 and an atomic weight of 24.31. Magnesium occurs in nature in compounds such as dolomite, magnetite, epsomite and carnallite. Due to its relatively low density (1.74 g/cm³), magnesium is widely used as a construction material. Other applications include production of alloys, steel industry, automotive construction, aviation and space technology, glass and cement manufacture, etc. [16]. In green plants, magnesium plays a central role, as photosynthesis does not proceed, when the metal has been removed from the chlorophyll molecule.

3.2.1 Dietary sources

Dietary sources rich in magnesium include whole grains, green leafy vegetables, tofu and nuts. Milk, legumes and potatoes are good sources of the metal. Plants are generally well endowed with magnesium due to its central role in photosynthesis [8, 9].

3.2.2 Absorption, metabolism and storage

The main site of magnesium absorption is the small intestine. Active transport, solvent drag and passive diffusion are the three mechanisms of magnesium absorption. Generally, 20–70% of ingested magnesium is absorbed in normal healthy humans [8]. Magnesium absorption could be affected by many dietary and physiological factors. While protein intake seems to increase magnesium absorption, fat supplementation has been shown to generate the opposite effect. In addition, high levels of phosphorous and calcium inhibit magnesium absorption. Magnesium is primarily stored in the bones (60–70%) and the remainder is evenly distributed between muscle and other soft tissue. Magnesium is excreted mainly in the urine or in feces [14].

3.2.3 Function

Magnesium has various physiological functions. Its is involved in more than 300 enzymatic processes in the body and plays an important role in skeletal mineralization and development, fatty acids synthesis, phosphorylation and dephosphorylation mechanisms, DNA and protein synthesis, insulin action in the liver, metabolic pathways for energy production, sodium and phosphorous metabolism and maintenance of transmembrane electrical potentials in nerves and muscle [1, 14].

3.3 Iron

Iron is a silvery-white metal classified second in the order of abundance of the elements in the earth crust after aluminum. It has an atomic number of 26 and an atomic weight of 55.8. It is mainly combined with oxygen in the crust forming iron oxide ores such as hematite, magnetite or limonite. Due to its interesting physico-chemical properties, iron is used in various domains such as steel industry, alloys, food fortification, environmental protection, bio-medical applications, etc. Iron is an essential element for almost all living organisms. It exists in the body in complex forms bound to protein as heme compounds (hemoglobin and myoglobin), heme enzymes, or nonheme compounds (transferrin, ferritin, and hemosiderin [14]). Iron deficiency anemia is the most common deficiency disorder in the world [8, 14].

3.3.1 Dietary sources

Organ meats such as liver and kidney, egg yolk, dried legumes, cocoa, cane molasses, and parsley are among the richest dietary sources of iron. Meat meals and fish meals contain lower iron amounts than blood meals. Generally, the bioavailability of heme iron found in animal products is better than that of nonheme iron found in vegetables or chlorophyll plants. Poor sources of iron include dairy products, fresh fruits and vegetables, white flour, white sugar and unenriched bread [1, 14].

3.3.2 Absorption, metabolism and storage

Generally, iron absorption increases with higher dietary intake of the metal. Only 5 to 15% of ingested iron is absorbed by human adults. However, this level may increase to twice or more in children and in deficient adults. The primary sites of iron absorption are the duodenum and the jejunum in the small intestine. Iron absorption is enhanced by ascorbic acid and cysteine dietary intake. However, tannins, phytates, egg yolk, tea, coffee, milk and soy proteins have an inhibitory effect on iron absorption [1]. Upon entering plasma, ferrous iron is oxidized to ferric form, then most of it binds to transferrin, and the rest to ferritin. Transferrin regulates iron body distribution by transporting more than 70% of plasma iron to the bone marrow for hemoglobin synthesis. The synthesized hemoglobin is then destroyed by phagocytes and the released iron is either returned to the circulation via plasma transferrin or stored as ferritin or hemosiderin. The liver, spleen, and bone marrow are the main sites of iron storage in the body [9]. Excretion of iron is done primary in feces and urine in addition to losses through sweat, hair, and nails [14].

3.3.3 Function

Almost *two-thirds* of body's iron is found in hemoglobin, a quarter is stored and most of the remaining 15% is in the muscle protein myoglobin. The primary function of iron is the transport of oxygen and carbon dioxide in the organism through red cells [1]. Iron is also a component of various enzymes required for energy production, immune system functioning or adenosine triphosphate (ATP) production.

3.4 Iodine

Iodine is a bluish black solid that belongs to halogen family including fluorine, chlorine and bromine. It has an atomic number of 53 and an atomic weight of 126.9. It is a relatively rare element in the earth's crust, which occurs in the dispersed state

in soil, water, air, and living organisms. There are many regions in the world low in iodine. This could be due to distance from the sea, low annual rainfall or recent glaciation [14]. Iodine is used in many industrial fields such as pharmaceuticals, medicine, metallurgy, lasers, herbicides, animal feeds, colorants, photographic equipment, etc. [8]. Iodine deficiency is one of the main cause of impaired cognitive development in children.

3.4.1 Dietary sources

The iodine content of food is highly dependent on the type of soil, climatic conditions and fertilizers. Hence, it is useless to give the concentration of dietary iodine in food composition tables since it is highly variable. Nevertheless, seafood, fish, seaweed and plants of the seaside are very rich in iodine. Fortified foods are also good iodine sources such as breakfast cereals or milk and milk products. The salt iodized with potassium iodate remains the most reliable source of iodine worldwide [1, 9].

3.4.2 Absorption, metabolism and storage

Iodine in water and food occurs usually as iodide or iodate compound. In these forms, it is rapidly absorbed in the gastrointestinal tract and circulates in the blood to all body tissues. Over 90% of ingested iodine is concentrated in the thyroid gland for adequate thyroid hormone synthesis or excreted in urine. If iodine supply is abundant, only 10% of iodine absorbed by the gut appears in the thyroid. However, this fraction may reach 80% or more, with long-standing iodine deficiency [14]. Iodine is stored in thyroid in the form of thyroglobulin, an iodinated glycoprotein that represent 90% of the total thyroid iodine. It is excreted either as organic iodine in the feces or as free iodine in the urine. Important goitrogen-containing foods include cassava, broccoli, cabbage, sprouts, kohlrabi, turnips, swedes, rapeseed, and mustard [8].

3.4.3 Function

Iodine is an essential constituent of the thyroid hormones thyroxine, and triiodothyronine. These hormones have multiple biological roles in thermo-regulation, reproduction, growth and development, intermediary metabolism, cell activity, and muscle function. Thyroid hormones also affect heart rate, respiratory rate, metabolism of carbohydrates and lipogenesis. In addition, they regulate proteins associated with cartilage metabolism, skin epidermis and hair production [8, 14].

4. Multivitamins and minerals as food supplements

4.1 Prevalence of use and associated factors

Vitamins and minerals are found in diets rich in fruits and vegetables. In the early 20th century, these micronutrients have been isolated, purified and manufactured as dietary supplements. Multivitamin/mineral (MVM) supplements, defined by the National Institutes of Health (NIH) as dietary supplements containing 3 or more vitamins and minerals, are the most commonly used type of dietary supplements among adults in the United States (US) [17]. According to the National Health and Nutrition Examination Survey (NHANES) 2011–2014 data

(n = 11,024), 52% of US adults took at least one dietary supplement in a 30-day period and MVM supplements account for the vast majority of total dietary supplements use [18]. MVM use was higher among women (34.0%) than men (28.3%) and the use raised linearly with age. Supplementation with MVM was particularly higher among older women (44.0%), non-Hispanic whites (35.7%), higher educated adults (36.3%), overweight adults (34.0%), former smokers (37.8%), moderate alcohol consumers (1 drink/day) (39.0%), adults with excellent or very good self-reported health status (36.7%) and those with private health coverage (35.1%) compared to their counterparts [18]. Perlitz et al. reported data on the use of vitamins and mineral supplements by adolescent living in Germany from the second wave of the German Health Interview and Examination Survey for Children and Adolescents (EsKiMoII), conducted from June 2015 to September 2017 [19]. They found that 16.4% of the adolescents (girls: 18.8%, boys: 14.0%) aged 12 to 17 years had consumed vitamin or mineral supplements in the previous four week. The use of micronutrients was higher among girls (18.8%) than boys (14.0%), normal weight adolescent (17.0%) than overweight ones (9.3%) and among adolescents with a high level of physical exercise (19.9%) than those with a low level of physical exercise (11.5%). Only one supplement, with both vitamins and minerals nutrients, was consumed by the majority of users. The most frequently used vitamin supplements were vitamin C (43.9%), followed by vitamin D (41.1%) and vitamin B₁₂ (30.4%). As regards mineral supplements, those containing magnesium (45.9%), zinc (28.1%), and iron (24.1%) were the most commonly consumed [19]. In Iran, the prevalence of dietary supplements use among children and adolescents was 34.1% [20]. Iron supplements were the most frequently used dietary supplements, with a prevalence of use of 12.9%, followed by multivitamins (8.1%) and vitamin D supplement (2.9%). Results showed that boys, children with excess weight and those with high-educated parents used less supplements compared to their counterparts [20].

Pregnant women are particularly vulnerable population groups and the MVM supplementation especially with iron and folic acid in pregnancy is highly recommended to improve birth outcome and to reduce low birth weight [21]. Data on MVM supplementation of pregnant women living in European countries revealed the presence of iron, iodine, vitamin A and zinc deficiencies, not only in low-income countries but also to an extent in Europe [22]. The inadequate intake among pregnant women may be due to poor knowledge about adequate nutrition, healthy vegetarian or vegan diets, special diets that avoid excessive weight gain, etc. [22]. Data on the dietary intake and mineral status of Polish pregnant women showed that 53.7% of pregnant women used supplements during pregnancy. Of supplement users, 93% took folic acid and only 16% consumed iron. Composite vitamin and mineral supplements were used by only 17.6% of Polish pregnant women [23]. Results of the NHANES 2007-2014 cross-sectional study revealed that 61.6% of American pregnant women used MVM supplements during pregnancy. However, the majority of this group do not consume the recommended amount of fruits and vegetables (five servings per day) [24].

4.2 Recommended intakes

Table 3 displays the recommended intakes of selected vitamins and minerals for men and women according to AFSSA (French Food Safety Agency), EFSA (European Food Safety Authority), IOM (Institute of Medicine) and WHO (World Health Organization) [25]. **Table 3** shows that several terms, referring to the population's nutritional references, are used by the different organisms. Hence, it is necessary to harmonize these terms.

Organism	Gender	VitA ²	VitB ₁	VitB ₂	VitB ₃	VitB ₆	VitB ₉	VitB ₁₂	VitC	VitD	Ca	Mg	Fe	I
AFSSA (RNI) ³	Men	0.80	1.50	1.80	17.40	1.80	0.33	0.0024	110	10	900	420	9	0.15
	Women	0.80	1.20	1.50	14.40	1.50	0.30	0.0024	110	10	900	360	16	0.15
EFSA (PRI) ⁴	Men	0.75	ND ⁵	ND	17.40	ND	0.33	0.0040	110	15	920	350	11	0.15
	Women	0.65	ND	ND	14.40	ND	0.33	0.0040	95	15	950	300	16	0.15
IOM (RDA) ⁶	Men	0.90	1.20	1.30	17.40	1.30	0.40	0.0024	90	15	1000	420	8	0.15
	Women	0.70	1.10	1.10	14.40	1.30	0.40	0.0024	75	15	1000	320	18	0.15
WHO (RNI)	Men	0.60	1.20	1.30	14.40	1.30	0.40	0.0024	45	5	1000	260	9.1-27.4	0.15
	Women	0.50	1.20	1.10	11.40	1.30	0.40	0.0024	45	5	1000	220	19.6-58.8	0.15

¹mg/day.

²Expressed in retinol equivalent (RE): 1 mg retinol = 1 mg RE; 1 mg β-carotene = 1/12 mg RE.

³Recommended Nutrient Intake.

⁴Population Reference Intake.

⁵Not Defined.

⁶Recommended Dietary Allowance.

Table 3.
Population's nutritional references of selected vitamins and minerals (mg/d).¹

4.3 Availability and regulatory status

MVM supplements can be obtained directly by the health care providers or purchased from retail stores such as pharmacies, grocery stores or health food stores. Many forms of vitamins and minerals and many routes of administration are available [13]. For example, vitamin D is manufactured as cholecalciferol or ergocalciferol and iodine is available as iodide or iodate [26]. Vitamin and mineral dietary supplements can be compounded in various ways and sold in capsules, pills, tablets, sachets of powder, ampoules of liquids and other similar forms of powder and liquids [13].

According to the Codex Alimentarius Guidelines for Vitamin and Mineral Food Supplements, the sources of vitamin and mineral supplements may be natural or synthetic and their selection should be based on considerations such as safety and bioavailability [27]. The minimum level of each vitamin and/or mineral contained in a vitamin and mineral supplement per daily portion of consumption should be 15% of the WHO recommended dietary intake. Moreover, the vitamin and mineral supplements must be packed in containers that are safe and suitable for their intended use.

4.4 Health effects

The use of MVM supplements is recommended in disease states, to correct deficiencies, or to promote health and protect from future chronic diseases in healthy subjects [28–31]. The main nutrient deficiency diseases prevalent in developing countries include *Xerophthalmia*, which is responsible of the blindness of over five million children suffering from visual impairment in the world [32]. According to Beaton et al. (1993), vitamin A supplementation reduces the mortality of children aged from six months to five years by 23% [33]. In addition, data showed a decrease in the prevalence of *Xerophthalmia* in children who regularly received vitamin A supplements, reaching 70% [32, 33]. In 1999, over 700 million people living in developing countries suffered from goiter and cretinism with severe brain damage and mental retardation [8]. An important progress was made with universal salt iodization including an approximate 13-point increase in intelligence quotient [32]. Iron deficiency anemia have adverse effects on the development of children as well as on the mortality and morbidity of infant and mother during pregnancy [8]. Research studies established that the use of iron supplements allowed a 20% reduction in mothers mortality [32]. In Nepal, the results of a demographic and health survey carried out in 2006 showed that in five years, the coverage of iron supplementation increased from 23–59%. These improvements, associated to additional measures, led to a reduction in iron deficiency anemia in pregnant women from 75–42% [34]. Zinc deficiency is associated to the incidence of serious childhood infectious diseases such as pneumonia and diarrhea, which causes 18% of deaths in children under five [35–37]. Zinc supplementation of children during acute diarrhea allowed the decrease of the illness duration by 9–23% [36]. In a community-based, double-blind, randomized trial conducted in India, zinc supplementation resulted in a 33% lower diarrheal incidence in children with low plasma concentrations [38]. During pregnancy, there is a high risk of fetal neural tube defects with folate deficiency. Research studies proved that folate intake by pregnant women reduced the risk of neural tube defects by 50% [32, 39].

5. Addition of vitamins and minerals to food

Vitamins and minerals are added to foods mainly to improve or maintain their nutritional quality. However, these nutrients are also used for other additive

Function	Vitamins and minerals
Antioxidants	Ascorbic acid, β -carotene, calcium ascorbate, ascorbyl palmitate, sodium ascorbate, tocopherols (mixed α , γ and δ), tocopherol (mixed natural concentrate)
Colourings	β -carotene, riboflavin, riboflavin-5'-phosphate, iron oxide, calcium carbonate
Flavor enhancers	Calcium chloride, magnesium sulfate
Floor additives	Calcium carbonate
Nutritive additives	Ascorbic acid, β -carotene, ascorbyl palmitate, calcium ascorbate, calcium carbonate, calcium lactate, cholecalciferol, ergocalciferol, ferrous sulphate, folic acid, magnesium oxide, nicotinic acid, retinol, riboflavin, retinyl acetate, thiamin, thiamin hydrochloride, thiamin mononitrate, α -tocopherol
Sequestrants	Calcium chloride, calcium citrate, calcium sulfate

Table 4.
Examples of use of vitamins and minerals as food additives.

functions (**Table 4**) [40]. Various forms of vitamin and mineral additives are commercially available such as powders, oily suspensions or emulsions [2, 40]. The most important factors affecting their stability include heat, oxygen, pH, moisture and light. For example, the stability of β -carotene and other provitamin A carotenoids is enhanced by ascorbic acid antioxidant, both in liquid or powder forms [41]. In addition, vitamin D is more stable when prepared in edible oils than in powder form. Preparations of vitamin D are usually provided in lightproof containers with inert gas flushing. The detrimental interactions between vitamins and minerals are also taken in consideration in the manufacture of these micronutrients, especially in liquid preparations. Some interactions between vitamins are advantageous such as niacinamide that act as solubilizer for riboflavin and folic acid [41].

6. Conclusion

Despite the essential role of vitamins and minerals in human's health, these micronutrients are not consumed in sufficient amounts in developing countries where millions of children die each year from micronutrients deficiency due to malnutrition. Therefore, additional efforts should be made worldwide to minimize disparities between developing and developed countries in the quality of nutrition.

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