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Biological properties of vitamins of the B-complex, part 2 – vitamins B_6 and B_7 (biotin, vitamin H)

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ABSTRACT

Vitamins B_6 (i.e., pyridoxin and its analogues) and B_7 (i.e., biotin or vitamin H) are essential molecules for many physiological processes. In addition to their well-known involvement in several enzymatic reactions, recent discoveries revealed their participation in other processes, e.g. in gene expression via epigenetic processes, including biotinylation of proteins in the case of biotin. Plants, fungi, archaea and most bacteria synthesize both vitamins, whereas animals and humans lack enzymes for their biosynthesis and depend on their exogenous supply. At least in case of biotin, human gastrointestinal microbiota can likely partly satisfy the need. Both vitamins are water soluble and require a transporter for efficient absorption after oral administration; they can be rapidly excreted, hence being considered largely non-toxic. In addition to physiological and kinetic aspects of vitamins B_6 and biotin, this review, which is based on a search in PubMed up to 2023, covers sources of these vitamins, the impact of food treatment on their content, causes and symptoms of deficiency and specific mutations related to their function. Currently available literature on the analytical determination of these vitamins in biological fluids, possible pharmacological uses, and symptoms of toxicity, although rare, are also included.

Keywords: pyridoxine; biotin; physiological; essential; toxicity

ABBREVIATIONS

AI	adequate intake
CoA	coenzyme A
GABA	gamma-aminobutyric acid
IL	interleukin
MCC	methylcrotonyl-CoA carboxylase
PLP	pyridoxal 5'-phosphate
PLPBP	pyridoxal phosphate-binding protein
PNPO	pyridoxine phosphate oxidase
SMVT	sodium-dependent multivitamin transporter
TNF-α	tumour necrosis factor α
TNSALP	tissue non-specific alkaline phosphatase

INTRODUCTION

Vitamins of the B-complex represent water-soluble molecules with essential roles in humans. The present review is a follow-up to our previous manuscript, in which we summarized the biological properties of the vitamins B_1, B_2, B_3 and B_5 [1]. Herein, we center on vitamins B_6 and B_7 (biotin) to provide a comprehensive summary of sources, properties, physiological functions, disorders that result from their deficiency and scientific information, which has been often overlooked since their discovery. We sought to cover all significant studies on the topic, including current trends and potential directions for future research. Such review has been previously missing in the available literature.

METHODS

PubMed was used as the bibliography database and eligible publications were selected from 1938 to 2023. The following keywords were added to the query box: (Vitamin B_6 AND properties) and (Vitamin B_6 AND sources) and (Vitamin B_6 AND pharmacokinetics), (Vitamin B_6 AND physiological function), (Vitamin B_6 AND pharmacological uses), (Vitamin B_6 AND toxicity). Instead of vitamin B_6 similar combination were used with pyridoxine, vitamin B_7, and biotin. The eligibility criteria were: peer-reviewed journal articles or book chapters published in the English language. There were no exclusion criteria for the search.

VITAMIN B_6

AN INTRODUCTION TO VITAMIN B_6

Vitamin B_6, geneally but imprecisely known as pyridoxine, is a general term for water-soluble pyridine derivatives with the same physiological role. This vitamin comprises six related compounds – vitamers (Figure 1A), i.e. mentioned pyridoxine (or pyridoxole, an alcohol), pyridoxal (an aldehyde), pyridoxamine (an amine) and their 5'-phosphate esters, such as pyridoxal 5'-phosphate (PLP), pyridoxamine 5'-phosphate and pyridoxine 5'-phosphate. PLP is the biologically active form of vitamin B_6 because it is a cofactor of most vitamin B_6-dependent enzymes in the organism [2, 3].

Pyridoxine was discovered in 1934 by Hungarian physician Paul György and colleagues, and it was isolated in pure form shortly thereafter. Humans must acquire it from diet. Moreover,

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PLP can be recycled from food and degraded vitamin B_6 in the salvage pathway when the vitamin undergoes interconversion inside the cells and yields different forms, including active PLP (Figure 1B) [4, 5]. Pyridoxine, pyridoxal and pyridoxamine are converted to their phosphorylated forms by the pyridoxine/pyridoxamine/pyridoxal kinase, while phosphatases hydrolyze phosphorylated vitamin B_6 vitamers. Pyridoxine 5'-phosphate and pyridoxamine 5'-phosphate are further oxidized to the active form, PLP by the enzyme pyridoxine (pyridoxamine) phosphate oxidase.

SOURCES OF VITAMIN B_6

Natural sources of vitamin B_6

Plants, fungi, archaea and most bacteria synthesize pyridoxine, whereas animals and humans lack enzymes for its biosynthetic pathway and rely solely on the exogenous supply of the vitamin [3, 6-27]. Vitamin B_6 is widely distributed in foods of plant and animal origin. Whole grains, bananas, potatoes, pulses, nuts, beef, pork, poultry, organ meats, and fish are good sources for humans [28-50]. Some herbs and spices (e.g., garlic, curry, and ginger)[51], some gluten-free pseudocereals (e.g., amaranth)[52], and royal jelly are also rich in vitamin B_6 [37, 53]. In animal-derived foods, vitamin B_6 is usually present in phosphorylated forms (mainly of pyridoxal and pyridoxamine) and, to a lesser extent, in the free one [23, 37, 54-56]. There is limited information on the bioavailability of vitamin B_6 from animal products in humans. The bioavailability is estimated to be generally high and, in many cases, almost complete. However, thermal processing reduces it by 25-30%; and the reaction between pyridoxal and pyridoxal phosphate with the ε-amino group of protein-bound lysine may be responsible for the decreased bioavailability [57-61]. In plant-derived foods, the vitamin usually occurs as both free pyridoxine and in a glycosylated form, particularly as pyridoxine-β-D-glucoside, whose proportion can range depending on the plant species, from 5% to 75% of the total vitamin content [23, 28, 54, 57, 62-68]. The glucoside is only partly cleaved enzymatically by hydrolases in the small intestine, and its bioavailability is about 50% and about 75% lower than that of free pyridoxine in humans and rats, respectively, i.e., apparently the capability of utilizing glycosylated form is species specific. The contribution of pyridoxine-β-D-glucoside to the total vitamin B_6 intake in the average human diet is around 15%, hence the different types of vegetarian diet does not pose a risk for vitamin B_6 deficiency. This fact is also supported by findings from a population-based survey comparing the vitamin B_6 status among vegetarians,

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pescatarians, flexitarians, and meat-eaters. However, individuals with a marginal intake of total vitamin B_6 would be more prone to reduced nutritional status due to this incomplete bioavailability [28, 29, 46, 54, 57, 58, 62, 64, 69-83]. The absolute bioavailability of vitamin B_6 from a mixed diet is estimated to be about 75% [29, 44, 84-86].

Vitamin B_6 is synthesized in significant quantities by the microbiota of the human large intestine as well and this could represent a secondary exogenous source of the vitamin. Indeed, the existence of a specific carrier-mediated mechanism for pyridoxine uptake in human colonocytes was demonstrated. On the other hand, it is likely that a large portion of the vitamin produced by microbiota is taken up by non-synthesizing microbes. The extent of the contribution of microbially produced vitamin B_6 to the overall body levels is unclear; there are no human studies to provide evidence for it [22, 28, 29, 37, 87-93]. Amounts of vitamin B_6 in some selected foodstuffs are shown in Table 1.

Antivitamins B_6

The diet can also contain antivitamins B_6 that either compete for reactive sites of vitamin B_6-requiring enzymes or directly inactivate the vitamin [37, 94]. The best-known antivitamin B_6 is probably ginkgotoxin (4'-O-methylpyridoxine), which occurs in different tissues of the tree *Ginkgo biloba*, with the highest concentrations being present in seeds. Ingestion of ginkgotoxin can lead to abdominal pain, epileptiform convulsions, and loss of consciousness due to the mentioned interference with vitamin B_6. As seeds are a food source in Southeast Asia, including China, Japan, and Korea, and extracts from leaves are used in pharmaceutical products worldwide, they represent a potential health risk [3, 95-112]. Indeed, ginkgotoxin and its derivatives found in the African trees of the genus *Albizia* (e.g., *A. tanganyicensis, A. versicolor*, *A. julibrissin*, and *A. lucida*) are the cause of poisoning of livestock (cattle and sheep); one of the most important agricultural problems in South Africa [3, 101, 113]. Flaxseed contains the vitamin B_6 antagonists, 1-amino-D-proline, and its precursor, the dipeptide linatine. Their possible deleterious effects through the consumption of flaxseed deserve attention in individuals with moderate vitamin B_6 status [94, 114-118]. Gyromitrin (N-methyl-N-formylhydrazone) from a toxic mushroom *Gyromitra esculenta* (genus *Gyromitra* is also known as false morrel) is converted to (mono)methylhydrazine after ingestion, which is able to inhibit pyridoxal kinase and hence depletes vitamin B_6. Intoxication usually occurs about 10 hours after the ingestion of fresh or dried mushrooms. It gives rise to poisoning

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symptoms such as confusion and seizures. Interestingly, during cooking, methylhydrazine volatilizes, and poisoning occurs also after inhalation of these vapours [118-122]. Similarly, agaritine containing a hydrazinic moiety in its structure is a toxic principle of various *Agaricus* species, e.g., edible button mushroom *Agaricus bisporus* [118, 121, 123]. The content of both toxins in fungi may be decreased by processing, such as boiling in water, drying, and freezing [121, 124, 125]. Other natural vitamin B_6 antagonists, which are of little significance to human nutrition, are toxic non-proteinogenic amino acids occurring in some leguminous plants: mimosine in *Mimosa* and *Leucaena* species, and canavanine and canaline in *Canavalia* species [118, 126-132].

Effects of food processing on vitamin B_6 content

Food processing is the transformation of agricultural products into foods for human consumption. Primary processing is the conversion of the inedible raw products into food ingredients. Secondary processing involves the conversion of food ingredients into edible foods. Tertiary processed foods are commercially prepared foods. Products from primary processes make up the major part of the human diet as they are either consumed raw or used as ingredients in secondary and tertiary processes [133]. Food processing may alter the vitamin B_6 content [134, 135]. A rough overview of major data on vitamin B_6 losses in some food groups due to processing is in the Table S1 in Supplementary data. More data on specific foods, information on conditions, and comments are in the text below.

Milling and refining of cereals

The primary processing of cereals (milling and refining) that separates the bran and germ, which are rich in micronutrients, from starchy endosperm causes considerable losses of vitamin B_6 [136-141]. Milling reduces the value of the vitamin B_6 content in maize by 65–75% [137, 142-146]. The vitamin B_6 content decreases by 66–89% in white wheat flour, compared to wholegrain one [45, 136-138, 142-144, 147]. The content of vitamin B_6 is likewise 64% and 79.5% lower in refined than in wholegrain rye and sorghum flour, resp. [144]. Vitamin B_6 losses in non-parboiled and parboiled white rice are 42–86% and 12–26%, resp., compared to brown rice. The decline in vitamin B_6 in parboiled rice is lower, in contrast to the non-parboiled one, because a part of the vitamin diffuses from the vitamin-rich outer bran layer into the endosperm during the parboiling process that takes place before milling [68, 137, 142, 143, 148-152].

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The secondary processing of cereals, such as breadmaking, rice cooking, and nixtamalization of maize, brings on additional vitamin B_6 losses. They are discussed below (Processing of plant-based foods).

Properties of vitamin B_6 and mechanisms of vitamin losses during food processing

Vitamin B_6 losses during processing and storage of food can occur in several ways. Being soluble in water, leaching is one of the principal causes. Vitamin B_6 in foods is stable under acidic conditions but unstable in neutral and alkaline environments, particularly when exposed to heat or light. The acidic aqueous solutions of vitamin B_6 may be heated without decomposition as vitamin B_6 is destroyed by ultraviolet radiation in neutral or alkaline solutions but not in acidic solutions. Vitamin B_6 is normally stable to oxygen. Of the several vitamers, pyridoxine is far more stable than pyridoxal and pyridoxamine. Therefore, the processing losses of vitamin B_6 tend to be highly variable, with plant-derived foods (containing mostly pyridoxine) losing little of the vitamin and animal products (containing mostly pyridoxal and pyridoxamine) associated with higher losses [37, 59, 87, 132, 134, 135, 147, 153-166].

Processing of animal-based foods

Boiling, stewing, roasting, and frying reduce the vitamin B_6 content by 55%, 33–58%, 30%, and 40–45%, resp., in pork, by 60–77%, 55–57%, 40%, and 55–58%, resp., in beef, and by 40–58%, 40–47%, 50% and 45–56%, resp., in chicken, depending on cooking temperature and time [161, 167-171]. In whole meat dishes, including cooking liquid, gravy, juice, or soup, about 15–20% more vitamin B_6 remains owing to retention of the vitamin leached into the water phase [168, 170, 172-174]. Fried breaded meats contain 5–35% more vitamin B_6 than those without breading, which may assist in trapping the liquid and, therefore, decreasing the loss of water-soluble vitamins [170, 175]. About 9% of vitamin B_6 was lost from pork and beef when the drip exuding from the frozen meat during thawing was discarded [176, 177]. The cooking loss of vitamin B_6 in fish meat (gilthead seabream, anchovy, and Atlantic bonito) was 55–85% and 60–89% when grilled and baked, resp., due to thermal degradation and leakage of the vitamin in the lost water [178]. Heat-induced reduction of vitamin B_6 in milk is usually 5–20%, 5–10%, 5–20%, 10–50%, and 40% for boiled, pasteurised, ultra-high temperature treated, sterilised, and condensed milk, resp., compared to raw milk [134, 170, 179-184]. Hard

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cooked, poached, scrambled, baked, and fried eggs lose during cooking 20–23%, 15%, 10%, 10%, and 10% of the vitamin B_6, resp. [170, 185, 186].

Processing of plant-based foods

Boiling, steaming, and frying lead usually to vitamin B_6 loss of 30–35%, 15%, and 10%, resp., in vegetables alone and to that of about 10%, taking total dish into account [168, 170]. In chickpeas, microwave cooking, autoclaving, and boiling caused a decline of 19%, 34%, and 42% in the vitamin B_6 content, resp. [187]. The amount of vitamin B_6 in potatoes is reduced by 30–57%, 21%, and 10% during boiling, baking, and deep frying, resp. [161, 169, 188]. The way of cooking rice influences the content of vitamin B_6. In different rice varieties, the boiling cooking method (cooking rice with extra water and then eliminating the water) led to vitamin losses of 3-74%, compared with the traditional cooking method (cooking with a constant amount of water without removing the water) [189]. During breadmaking, the vitamin B_6 content decreased on average by 33% and 62% in whole and white wheat bread, resp., in comparison to the whole and white wheat flour [190, 191]. Similar results were obtained during rye sourdough bread production [192]. Toasting wheat bread induced an increase in vitamin B_6 by 75% due to its release from glycosidic bound forms [191]. Effects of extrusion techniques on vitamin B_6 retention in cereal grains showed a reduction by 0–23% and by 65% in maize grits and oat whole grains, respectively [193]. Drying of tarhana, a traditional Turkish fermented cereal food, resulted in vitamin B_6 losses of 3%, 16%, and 23% at temperatures of 50°C, 60°C, and 70°C, resp. [194]. A decrease in vitamin B_6 content in nuts varied from 2–7.5% in almonds up to 4–34% in pistachio nuts after roasting [195, 196]. Alkali-processing of corn grains to masa (nixtamalization) resulted in a loss of 23% vitamin B_6 [145]. The highly variable content of vitamin B_6 in beer is affected by several factors, including raw materials and the brewing process [197-199]. Germination is an effective way to improve the nutrition value of edible seeds: increases of 54%, 78%, and 26% in the vitamin B_6 content occurred in germinated lentils[200], rough rice[201], and faba beans[202], resp. On the other hand, the vitamin B_6 levels decreased by 11%, 13%, and 50% in germinated wheat[203], brown rice[201], and sorghum[204], resp., after germination.

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Food preservation and storage

Canning, a food conservation method, brought on vitamin B_6 reduction of 46%, 34%, 31%, and 18% in mushrooms, whole peeled tomatoes, white asparagus, and lentils, compared to the respective unprocessed products [205]. Ionizing irradiation, a method used for food preservation, has a low effect on vitamin B_6; losses ranging from zero in wheat to about 15% in fish were observed [206, 207].

The amount of vitamin B_6 in button mushrooms significantly declined by 23% and 45% after 6 and 12 months, resp., during frozen storage at - 20°C [208]. The content of vitamin B_6 decreased gradually in aseptically packaged ultra-high temperature treated milk during storage at room temperature, resulting in a 96% loss after 20 weeks [183]. No remarkable changes and a 20% decline in the vitamin B_6 content happened in vacuum-packaged broccoli au gratin and salmon, resp., stored at room temperature either on the Earth or exposed to spaceflight for 880 days; the vitamin from flight samples did not degrade faster than that from ground controls [209]. The investigation of the influence of storage conditions on vitamin B_6 retention in the freeze-dried tuna mornay meal (containing tuna, vegetables, and pasta) fortified with that vitamin showed a mean decrease of 14% in the vitamin following storage at temperatures of 1°C, 30°C, and 40°C for up to 24 months [210]. The vitamin B_6 losses in meals in two hospital foodservice systems, the cook/hot-hold one, where food is held hot from the time of cooking to service, and the cook/chill one, where the cooked food is chilled, stored, and reheated, have also been summarized and compared [211].

Industrial production of vitamin B_6

Pyridoxine hydrochloride, which is mainly used in pharmaceutical preparations, dietary supplements, and as an additive in food and feed, is manufactured by chemical synthesis [29, 37, 60, 84, 87, 158, 212-219]. All present-day industrial vitamin B_6 syntheses use the Diels-Alder reaction of a diene (4,5-substituted oxazoles) and a dienophile (alkyldioxepins) as a key step [158, 220-225]. An alternative to the current chemical processes might be environmentally sustainable bioprocesses based on the microbial vitamin B_6 fermentation, which is of great interest to the biotechnological industry. Several attempts have been made to construct overproducing strains by genetic engineering of microorganisms like *Sinorhizobium meliloti*, *E. coli*, and *Bacillus subtilis*. Unfortunately, production levels are too

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low for being cost effective. Therefore, major metabolic engineering efforts are still required for developing fermentation processes that could outcompete the chemical synthesis of vitamin B_6. The main bottlenecks are insufficient activities of some enzymes in the biosynthetic pathway and accumulation of toxic intermediate metabolites [226-237].

Food fortification and biofortification with vitamin B_6

Food fortification is defined as the practice of deliberately adding an essential micronutrient to the food that is commonly consumed by the general population with the intention of improving the nutritional quality of the food supply and providing a public health benefit with minimal risk to health [238-240]. Foods fortified with vitamin B_6, similarly to dietary supplements, constitute an additional dietary source of the vitamin [60, 150, 241-246]. Overall, vitamin B_6 deficiency is rare in the general healthy population [8, 29, 44, 150, 243, 246-250]. It may be a concern in high-income as well as low-income countries in certain groups [142], such as older adults [245, 251-254] people of low socio-economic status, and those experiencing food insecurity [142, 241, 244, 245, 250]. As for 2022, some countries, mostly but not solely located in Africa, have mandatory fortification of wheat flour (most often), maize flour, and/or rice with vitamin B_6 (Nicaragua, Panama, Cuba, Peru, Jordan, Palestine, Nigeria, Chad, Ethiopia, Kenya, Uganda, Rwanda, Burundi, Tanzania, Mozambique, Zimbabwe, and South Africa) [255-257]. There is a voluntary fortification with vitamin B_6 in many other countries, such as the United States of America, the Dominican Republic, Eswatini, India, Bangladesh, Myanmar, the United Kingdom, and countries of the European Union; the vitamin is added to various foods, such as atta, maida, rice, breakfast cereals, beverages, and cereal-based foods for infants and young children [28, 60, 142, 150, 217, 255, 256, 258-265].

Biofortification is a process of increasing the density of micronutrients (vitamins and minerals) in a crop and comprises (*sensu stricto*, i.e., omitting agronomic practices) conventional plant breeding and genetic engineering approaches. It differs from fortification because it aims to make plant foods naturally more nutritive rather than adding nutrients to the foods during the food processing. Biofortification is an ideal strategy to improve nutrition for rural and poor communities that rely on subsistence farming for nutrition or may not have access to diverse diets, supplements, and fortified foods. Biofortification complements existing interventions and may help by increasing the daily adequacy of micronutrient intakes among the most vulnerable micronutrient deficient people [142, 239, 266-268]. Vitamin B_6 is *de novo* synthesized by plants, and therefore, biofortification could be a promising route to

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enhance food quality by increasing the vitamin levels in plants in the future [8, 269-271]. Analysis of the natural diversity of vitamin B_6 content in wheat, rice, and potato germplasm has shown limited variation, so breeding strategies do not seem to be adequate to increase the vitamin content in those crops[68, 142, 272, 273], in contrast to maize, where remarkable wide ranges in vitamin B_6 levels among various genotypes was recently reported [274]. Most efforts to date have used genetic engineering approaches. Biosynthesis of vitamin B_6 is primarily controlled by two enzymes making vitamin B_6 biofortification an attractive target for plant geneticists. Overexpression of genes encoding one or both enzymes leads to the enhanced accumulation of vitamin B_6 in transgenic plants, compared to the untransformed ones: 0.86-1.25-fold in tobacco plant, 1.45-4-fold in Arabidopsis seeds, 0.16-34.96-fold in wheat seeds, 1.6-3.9-fold in rice seeds, 3-16-fold in cassava roots, and 1.07-1.5-fold in potato tubers. Interestingly, enhancing vitamin B_6 levels in plants may also positively affect their tolerance to environmental stress [27, 142, 268-270, 275-280]. All the biofortification attempts revealed the feasibility of raising the vitamin B_6 amounts in plants. So far, the vitamin B_6 contents in transgenic plants are low and highly variable. Regardless, more research for understanding the regulatory mechanisms that control genes involved in the biosynthesis and metabolism of vitamin B_6 in plants is needed [225, 269].

PHARMACOKINETICS OF VITAMIN B_6

The total content of vitamin B_6 in the adult human body is about 170 mg [281]. Vitamers B_6 are absorbed in the upper small intestine (jejunum) from diet and/or oral supplements. In addition to the dietary source of the vitamin, humans might also receive vitamin B_6 from the bacterial microbiota in the large intestine as mentioned above [88, 282, 283]. All vitamin B_6 analogues i.e. pyridoxine, pyridoxamine, and pyridoxal are present in the diet. Phosphorylated forms undergo dephosphorylation by the means of phosphatases prior absorption into epithelial cells and prior release into the portal system. Phosphorylated forms are poorly diffusible and, in fact, they are trapped in the cells and a dephosphorylation step is necessary for their efflux. The bioavailability of vitamin B_6 from supplements is about 95%, whereas the bioavailability of pyridoxin, pyridoxal and pyridoxamine is similar. The presence of fiber in plant sources reduces bioavailability by 5-10%, while the presence of pyridoxine glucoside reduces bioavailability by 75-80%. On average, the bioavailability of vitamin B_6 from a mixed diet can be estimated to be about 75%. In fact, absorption in the intestine is mediated both via passive diffusion (i.e. large amount is readily absorbable without cell

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saturation) and a carrier mediated mechanism (i.e. saturable mechanism). In humans, there is carrier-mediated transport of B_6 vitamers *via* the vitamin B_1 (thiamine) transporters THTR1 and THTR2, which belong to the SLC19A2 and SLC19A3 families [284]. The maximum concentration (C_{max}) of pyridoxine is usually achieved within 5.5 hours [285, 286]. In the liver, all forms of dephosphorylated vitamin B_6 are rephosphorylated and finally converted to pyridoxal 5'-phosphate in the hepatocytes. Several enzymes, such as ATP-dependent pyridoxine/pyridoxamine/pyridoxal kinase, phosphatases and flavin mononucleotide-dependent pyridoxine phosphate oxidase (PNPO) are involved in these reactions. PNPO converts pyridoxine 5'-phosphate (PNP) and pyridoxamine 5'-phosphate (PMP) into pyridoxal 5'-phosphate (PLP) (Figure 1B).

Pyridoxal phosphate further binds to albumin in the liver, and it is released into the circulation, where it forms approximately 60 % of total circulating B_6 with lesser amounts of all three dephosphorylated forms. After dissociation from albumin and dephosphorylation by alkaline phosphatase, free pyridoxal is taken up by erythrocytes and then trapped inside cells in the form of PLP [287-292].

Plasma PLP is the most common parameter for determination of vitamin B_6 status. Its usual concentration is more than 30 nM in adults [5]. PLP is utilized as a cofactor of many enzymes related to a row of metabolic pathways [293, 294] as will be discussed below. Circulatory PLP passes into breast milk, crosses also physiological barriers such as placental and blood-brain barriers. The same mechanism as in other organs is described for the brain entry and storage, i.e. initial dephosphorylation in the blood-brain barrier by the means of tissue non-specific alkaline phosphatase (TNSALP) followed by uptake and entrapping of the vitamin in neurons after phosphorylation to PLP [295].

The major inactive metabolite of PLP is 4-pyridoxic acid. It is formed in the liver and excreted in the urine (Figure 2). Urinary excretion of this metabolite greater than 3 mmol/day can be used as a marker of adequate short-term vitamin B_6 status. Its half-life appears to be 15–20 days [296].

Although there is not a large storage of vitamin B_6 in tissues, probably due to the fact that human organism requires only small amounts of vitamin B_6 from food sources since the biologically active form PLP can be formed not only by interconversion from different B_6 vitamers, but also using the cofactor from degraded enzymes in the salvage pathway.

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PHYSIOLOGICAL FUNCTION OF VITAMIN B_6

The active form of vitamin B_6, PLP, acts as a coenzyme in more than 140 different enzymatic reactions necessary for vital cellular processes [8]. This function is enabled by the highly reactive aldehyde group of PLP, that forms Schiff bases with ε amino group of lysine residue at the active centre of PLP dependent enzyme. On the other hand, binding to lysine residues on some hormonal receptors is responsible for transcriptional modulation. Moreover, the aldehyde group can react with other amino acids in proteins, especially with cysteine or histidine [297].

PLP is involved in various pathways, such as:

- Some steps during the metabolism of amino acids, e.g. transamination, decarboxylation, and racemization processes. Metabolic transformation of sulphur-containing amino acids, e.g. the conversion of methionine to cysteine through the key intermediate homocysteine or S-adenosylmethionine. Elevated levels of circulating homocysteine in the blood are associated with an increased risk of cardiovascular diseases, and S-adenosylmethionine is a methyl donor for many methylation reactions, e.g. methylation of proteins, DNA and RNA and others [298-301]. In addition, cysteine synthesized by this transsulfuration pathway is an important contributor to glutathione synthesis, which plays a role in oxidative stress and the antioxidant defense system.
- Some processes during carbohydrate metabolism, e.g. degradation of stored carbohydrates such as glycogenolysis, when PLP is a cofactor for glycogen phosphorylase. PLP also plays a role in the reactions that generate glucose from amino acids in the process known as gluconeogenesis [302-304].
- Lipid metabolism, especially biosynthesis of sphingolipids, which are important for myelin formation, and their breakdown [305].
- Biosynthesis of many neurotransmitters, particularly the formation of serotonin from tryptophan and the synthesis of epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine (3,4-dihydroxyphenethylamine) from phenylalanine and tyrosine. PLP also controls the formation and regulation of the inhibitory transmitter γ-aminobutyric acid (GABA) in the brain and the neuromodulator serine [84, 306-309].
- Catabolism of tryptophan and its conversion to niacin, that requires enzyme kynureninase, also necessitates vitamin B_6 [310-313].

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- Biosynthesis of tetrapyrroles (e.g. heme). PLP is needed for the enzymatic reaction using succinyl-CoA and glycine to generate δ-aminolevulinic acid, an intermediate precursor in tetrapyrrole biosynthesis [314, 315].
- Immune and inflammatory pathways, especially regulation of cytokine production, particularly interferons and interleukin 6 [316, 317].

Besides the role of PLP as a cofactor in biochemical reactions, vitamin B_6 also plays other important roles in non-enzymatic functions, e.g.,

- PLP inhibits enhancement in gene expression by steroid and thyroid hormones, and vitamins A and D by binding to lysine residues in the hormone-receptor complexes [318, 319].
- Antioxidative activity by scavenging reactive oxygen species and chelating of redox-active metal ions [320-322].

VITAMIN B_6 DEFICIENCY AND RELATED DISORDERS

Severe vitamin B_6 deficiency resulting from inadequate intake (especially from dietary deficit) is rare in the healthy general population. Hypovitaminosis is usually found in association with other B vitamin deficiencies, such as those of folic acid (vitamin B_9) and vitamin B_{12}. As aforementioned, it should be emphasized that dietary vitamin B_6 deficiency can occur in elderly people (aged 65 years and over) [323]. Secondary vitamin B_6 deficiency is mostly a result of genetic disorders or drug interactions [324, 325].

Due to involvement of vitamin B_6 in many metabolic pathways, lack of sufficient amount of vitamin B_6 vitamers causes various biochemical changes and may lead to significant health problems. In particular, PLP is essential in the synthesis and metabolism of amino acids and neurotransmitters. Loss of function of PLP-dependent enzyme glutamate decarboxylase leads especially to decreased levels of the inhibitory neurotransmitter GABA.

Vitamin B_6 deficiency in humans is associated with seborrheic dermatitis and cheilosis (including cracks at the corners of the mouth), glossitis with ulceration, anaemia, sensory polyneuropathy, depression, decreased immune function and increased risk of cardiovascular diseases. In children, characteristic symptoms of deficiency are abnormalities in hearing and seizures.[84] Seizures are the results of an imbalance between excitatory (glutamate) and inhibitory (GABA) neurotransmitters [326-328].

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In the population, there are certain groups of people at increased risk of vitamin B_6 inadequacy. People with impaired absorption especially due to malabsorption syndromes (usually associated with Crohn´s disease and ulcerative colitis) and after bariatric surgery have low vitamin B_6 levels. Patients with renal disease, predominantly with chronic renal insufficiency undergoing dialysis, and liver disease tend to have low plasma PLP concentrations. Also, alcoholics need vitamin B_6 supplementation because alcohol is metabolized to acetaldehyde, which decreases PLP formation in cells and competes with PLP for protein binding. Additional groups at risk of vitamin inadequacy despite adequate dietary intakes are not solely elderly persons but also those with autoimmune disorders (e.g. rheumatoid arthritis), who are obese and in pregnancy or who are taking oral contraceptives [329-332]. Analytical methods for the detection of vitamin B_6 are summarized in Table 2. More details are shown in Supplementary Data Table S2, which evaluates individual specific methodologies with the relevant citation from which the information was obtained

Pyridoxine-dependent epilepsy

Pyridoxine-dependent epilepsy (pyridoxine-dependent seizures, vitamin B_6-responsive epilepsy) is a rare inherited metabolic disease characterized by recurrent seizures with their onset usually in prenatal, neonatal, and postnatal period or in childhood. Seizures are caused primarily by low levels of GABA due to PLP deficiency, nevertheless, other abnormalities are involved, e.g. low levels of adenosine and methionine cycle defects. This type of epilepsy responds to high intravenous doses of vitamin B_6, either as pyridoxine or as its active form PLP, but are resistant to conventional antiepileptic drugs [333]. Decreased PLP availability in this disease is caused by mutations in some genes involved in vitamin B_6 metabolism, e.g.,:

- Mutation in ALDH7A1, a gene encoding antiquitin, the enzyme with α-aminoaddipic semialdehyde dehydrogenase activity, involved in lysine degradation. Antiquitin deficiency leads to the accumulation of the toxic lysine intermediates α-aminoadipic semialdehyde and 1-piperideine-6-carboxylic acid, inactivating PLP by chemical complexation [334-336].
- Mutation in ALDH4A1 gene occurring in metabolic disease hyperprolinaemia II causes the formation of pyrroline-5-carboxylate, a compound structurally similar to 1-piperideine-6-carboxylic acid, that leads to the inactivation of PLP as well [337, 338].
- Mutations in PNPO gene influencing PLP recycling and synthesis [339-341].

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- Mutations in the pyridoxal phosphate-binding protein (PLPBP) gene (formerly called proline synthetase co-transcribed homolog). PLPBP protects PLP from damage by intracellular phosphatases [342-345].
- Mutations in the ALPL gene encoding tissue non-specific alkaline phosphatase (TNSALP) in metabolic disorder hypophosphatasia [346].
- Mutations in the PIGV, PIGO and PGAP2 genes responsible for the development of hyperphosphatasia with seizures and neurologic deficit (Mabry syndrome). These genes play a crucial role in the production of glycosylphosphatidylinositol anchor, that binds TNSALP to the cell membrane. Mutations result in the production of unfunctional glycosylphosphatidylinositol anchor and subsequent release of TNSALP in the blood (= hyperphosphatasia) [347].

These metabolic diseases associated with defects in vitamin B_6 are summarized in Table 3.

CLINICALLY USED DRUGS AS ANTIVITAMINS B_6

In addition to natural antivitamins B_6, there are also certain clinically used drugs having the same effect. Drugs such as theophylline (a bronchodilator used in the treatment of respiratory diseases, e.g. asthma) and caffeine (psychostimulant) directly inhibit pyridoxal kinase, enzymes involved in activation of PLP. In the case of caffeine, such effects are probable solely in intoxication. The result is a PLP deficiency with accompanying reduction in PLP-dependent enzymes activities and known consequences including neurotoxic reactions, e.g. peripheral neuropathy, restlessness, agitation, tremor and seizures [348-350]. It should be mentioned that standardized extract from *Ginkgo biloba* are easily available and used in the therapy of a number of conditions, such as peripheral circulatory disturbances, dizziness, tinnitus, etc. [98, 351, 352]. Hydrazine derivatives includes, beyond aforementioned gyromitrin, also antituberculosis drug isoniazid (isonicotinic acid hydrazide). Administration of this drug, in particular in overdose, results not only in the inhibition of pyridoxal kinase by the isoniazid metabolite (hydrazone), but also the inactivation of PLP occurs by other isoniazid metabolites (hydrazines and hydrazides), that form e.g. isonicotinilhydrazide, a compound that is easily excreted in the urine [353]. Another antituberculosis drug cycloserine reacts with PLP forming covalent complexes that might inhibit pyridoxal kinase [354]. Another group of drugs, including penicillamine and levodopa, form complexes with PLP, but they do not inhibit pyridoxal kinase [355, 356]. Additionally, antiepileptic drugs (phenytoin, valproic acid,

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carbamazepine) increase metabolism of vitamin B_6 vitamers, resulting in low PLP plasma levels [357].

DIETARY RECOMMENDATION AND PHARMACOLOGICAL USE OF VITAMIN B_6

Vitamin B_6 is available in both multivitamin preparations with other B vitamins but also as a single vitamin preparation. Oral tablets or solutions for parenteral (intravenous, intramuscular) administration are the most common forms; they usually contain pyridoxine hydrochloride or sometimes PLP.

In adults, the current recommended dietary allowances range between 1.3–2.0 mg/day. During pregnancy, lactation and elderly, the requirement is increased [286]. Recommendations for pyridoxine intake according to age and gender are listed in Table 4.

As a supplement, vitamin B_6 is used especially in cases of its deficiency, which may be due to insufficient intake or increased need, as specified above. As a medication, pyridoxine or PLP are given prophylactically or therapeutically to patients with pyridoxine-dependent epilepsy. In newborns with hereditary syndrome, it is necessary to administer this vitamin in the first week of life to prevent mental retardation or anaemia, and lifelong therapy is necessary. In the literature, however, there is a lack of congruence regarding dose recommendations. The optimal dosage should ensure control of epileptic seizures, and, at the same time, the absence of side effects in a particular patient. In fact, adequate dosage of pyridoxine requires an individualized regimen according to the desired goal of therapy and tolerance of adverse effects.

Higher doses of pyridoxine are initially administered, e.g. in newborns 200 mg/day orally, and are usually gradually reduced to a tolerated level as part of maintenance therapy, e.g. 50-100 mg/day, after one week. Oral therapy with the active metabolite PLP is also successful in some types of seizures, e.g. due to the mutations in PNPO. Vitamin B_6 might improve certain congenital PLP-enzymopathies such as cystathioninuria, homocystinuria with accompanying vitamin B_6 deficiency [286, 333, 339, 358].

Pyridoxine is also used as an antidote, in cases of overdose with antivitamins B_6, such as isoniazid, cycloserine, penicillamine and in cases of poisonings with *Gyromitra* mushroom and *Ginkgo biloba* seeds. It is also recommended in ethylene glycol poisoning, because, as a cofactor, it is able to improve the conversion of glyoxylic acid, a toxic metabolite, into glycine [359]. Vitamin B_6 is sometimes given prophylactically in drug-induced deficiencies (e.g. due to isoniazid) to prevent the development of peripheral neuritis [360].

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In addition, this vitamin can be prescribed for the treatment of a number of other health conditions associated with vitamin B_6 deficiency including sideroblastic anaemia [315]. Supplementation reduces the risk of cardiovascular diseases as vitamin B_6 seems to have cardiovascular protective effects *via* mechanisms related to homocysteine, tryptophan-kynurenine pathways and increased levels of carnosine or anserine, which have antioxidant and anti-inflammatory properties [361]. Furthermore, pyridoxine is used empirically, e.g. in nausea and vomiting during pregnancy, premenstrual syndrome, carpal tunnel syndrome, and rheumatic arthritis [362-364].

Recent studies indicate that vitamin B_6 exerts also anti-inflammatory and anti-apoptotic effects and may have a beneficial effect on preventing diseases linked to inflammation (e.g. rheumatoid arthritis, acute pancreatitis, cardiovascular diseases, psoriasis) or could be an effective therapeutic agent in this field. Although the connection between vitamin B_6 and inflammation is evident, the specific mechanisms involved often remains unclear. Identification of potential therapeutic targets, signaling pathways, inflammatory markers provides a valuable foundation for further research in this area [365-369].

TOXICITY OF VITAMIN B_6

Because vitamin B_6 is a water-soluble compound not substantially stored in the body, redundant amounts are quickly excreted in the urine. Hence, its low potential toxicity is anticipated. Indeed, it is not possible to get toxic levels of vitamin B_6 through diet from food sources. Taking supplements of vitamin B_6 in appropriate doses (see Table 4) is considered to be relatively safe. Mild adverse effects include nausea, headache, fatigue and drowsiness; dermatological lesions can be observed [370]. However, toxicity can occur after long-term administration of supplements with high vitamin B_6 content. Therefore, a daily tolerable upper intake level for safe dosage was introduced by the European Food Safety Authority [371]. The tolerable upper intake level of vitamin B_6 for adults is 12 mg/day (including pregnant and lactating women) and in children 1-3 years old: 3.2 mg/day, 4-6 years old: 4.5 mg/day, 7-10 years old: 6.1 mg/day, 11-14 years old: 8.6 mg/day and 15-17 years old: 10.7 mg/day.

Long-term supplementation with doses above the tolerable upper intake level may result primarily in peripheral neuropathy with neurological symptoms including pain in extremities, muscle weakness, ataxia, and paraesthesia. Symptoms of toxicity are reversible after withdrawal, but some signs may still persist for 3-6 weeks. Paradoxically, these neurological

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symptoms of polyneuropathy after supplementation of high doses are similar to those of vitamin B_6 deficiency. High levels of pyridoxine (inactive form) are thought to inhibit pyridoxine-phosphate dependent enzymes by competing with the biologically active form of vitamin B_6, i.e. PLP. Vitamer, that is responsible for neurotoxicity is pyridoxine, because it competitively inhibits GABA neurotransmission, which may lead to neurodegeneration [372-375].

BIOTIN–VITAMIN B_7

AN INTRODUCTION TO BIOTIN

Biotin, also known as vitamin B_7 or vitamin H, is water-soluble and an essential micronutrient for all organisms. The first observations related to biotin occurred in 1916 when English biochemist W. G. Bateman identified a condition characterized by neuromuscular symptoms, severe dermatitis, and hair loss in rats fed a diet in which the only source of protein was raw egg white [376]. Cooking of egg or administering yeast or liver to rats was able to revert this syndrome. Later, in 1936, Kögl and Tönnis isolated a factor present in egg yolk that was essential for yeast growth, and they named it biotin. Subsequent findings revealed that biotin was responsible for the protection against egg white toxicity, and this toxicity was attributed to avidin**,** a glycoprotein found in raw egg white that binds to biotin with very high affinity and prevents its absorption [376, 377].

Humans obtain biotin from both food and *via* bacterial synthesis in the large intestine. Biotin is a cofactor for five carboxylases involved in metabolic processes [378]. Other functions include biotinylation of histones, gene regulation and cell signalling [379].

CHEMICAL STRUCTURE AND ADEQUATE INTAKE LEVEL

In 1942, Vigneaud and his colleagues identified the chemical structure of biotin (Figure 1C). Biotin can exist in eight stereoisomers, but D-biotin is the solely biologically active stereoisomer. At physiological pH, biotin exists mainly in its anionic de-protonated form because its pKa is 4.5 [380, 381].

In the 30s of the 20th century, experiments on biotin biosynthesis started with studies about the nutritional requirements of microorganisms [382]. Eisenberg et al. explored the pathway of biotin biosynthesis in *Escherichia coli* [383, 384]. In fact, certain microorganisms like mentioned *Escherichia coli* but also *Staphylococcus aureus* synthesize biotin. In these

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microorganisms, biotin is synthesized by enzymes encoded in the *bio* operon, whose transcription is regulated by the biotin retention protein A. This protein acts as both a biotin-dependent transcriptional repressor that regulates biotin biosynthesis and an enzyme that catalyses the attachment of biotin to biotin-dependent enzymes [385].

Interestingly, there are differences among bacterial species. For instance, *Staphylococcus aureus* responds to environmental biotin and grows when a media is supplemented with biotin, while *Mycobacterium tuberculosis* obtains biotin only through its synthesis *de novo* [386]. In contrast, animal cells are not capable of synthesizing biotin by their own enzymes. Hence, biotin must be absorbed from the diet.

When analysing biotin content in different foodstuffs, it is necessary to consider that values vary according to the origin of foods and the methodology used to determine biotin. HPLC/avidin-binding assay has a higher specificity than a microbiological assay. The latter method tends to overestimate biotin content [387].

In the 80s, doses of 35 μg/day for infants and 150–300 μg/day for adults were considered safe. Despite decades of investigation, there is still no consensus about the ideal daily intake of biotin [388]. Nonetheless, the World Health Organization (WHO) established adequate intake (AI) levels for humans dependent on life stage and gender (Table 5) [389]. AI for adults ranges between 30 and 40 μg/day. In the case of breastfeeding women, an additional 5 μg is required to compensate for the needs of this stage [389, 390]. European Food Safety Authority (EFSA) recommends higher values, namely 40 μg/day for adults and pregnant women and 45 μg/day for breastfeeding women. In the case of children (1- to 17-year-olds), AIs also increase with age, ranging from 20 to 35 μg/day (Table 5) [390].

Human bacterial microflora in the large intestine is also an important source of biotin for humans. However, its quantitative contribution remains unknown [380]. Interestingly, around 30% of the gut microbes cannot synthesize biotin even if it is essential for them [391]. Regardless, the microbiota in the human large intestine synthesizes significant amounts of biotin because biotin faecal excretion has been observed to exceed its dietary intake. Identification of a specific carrier-mediated mechanism for biotin uptake in human-derived colonic epithelial cells *in vitro* has been reported. It could locally contribute to the nutritional needs of the colonocytes, but it does not seem to contribute principally to the total quantity of absorbed biotin. This is supported by some observations, e.g., urinary excretion varies with biotin dietary intake whereas faecal excretion is independent of it. On the other hand, it has recently been reported that bariatric surgery is associated with an increased abundance of

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bacterial biotin producers in the gut and improved systemic biotin status in humans. Thus, it is still controversial and unclear if and to what extent biotin produced by gut microorganisms can contribute to meet human needs for this vitamin. Moreover, the contribution of microbial biotin synthesis in the gut has never been quantified. It is considered that biotin requirements must be met mainly by diet [22, 80, 88, 90-93, 283, 392-406].

SOURCES OF BIOTIN

Natural sources of biotin

Biotin biosynthesis occurs in bacteria, archaea, plants, and fungi. Animals and humans, as well as many protozoa, cannot synthesize the vitamin and depend on its exogenous supply [14, 22, 26, 93, 385, 407-457]. In the human diet, biotin is present in many foods in variable amounts. Major dietary sources include eggs, or precisely egg yolk, milk and dairy products, nuts (e.g., almonds, peanuts, and walnuts), legumes (soybeans and lentils), mushrooms, some vegetables (e.g., cauliflower, cabbage, broccoli, spinach, and sweet potatoes), cereals, meat, and some fruit (e.g., avocados, raspberries, and bananas). Yeast and offal (liver and kidney), in addition to egg yolk, are very rich in biotin (Figure S1) [30, 40, 83, 152, 188, 387, 393-395, 397, 399, 447, 458-472]. It has also been observed that the biotin nutritional status of both lactoovovegetarians and vegans is not impaired compared to people consuming a mixed diet [473].

Biotin in foods is found as free biotin and as biocytin (biotinyl-lysine) bound in proteins. After proteolysis, biotin is released from biocytin by biotinidase, located in pancreatic juice and intestinal mucosa. The proportion of free and bound vitamin forms varies among foods. For example, the majority of biotin in meats, yeast, and cereals appears to be protein-bound; in milk, however, the vitamin occurs nearly exclusively in the free form. At present, there are no reliable data on the average bioavailability of biotin from a usual mixed diet. Experiments using pharmacologic doses of free biotin revealed a bioavailability of biotin approaching 100%. Also, human kinetic study showed that intravenous administration and oral administration may have the same urinary recoveries. There is, however, a lack of data on the degree of biotin absorption from the protein-bound form [80, 392-397, 399, 464, 474, 475]. Data on the biotin content in foods is limited and is not ordinarily published in different food composition databases (e.g., in the USDA National Nutrient Database for Standard

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Reference). Both natural variation and analytical aspects may account for the sometimes reported high variability of biotin contents [387, 393, 395, 396, 398, 466, 470, 476]. Biotin amounts in some selected foodstuffs are summed up in Table 6.

A natural antagonist of biotin – avidin

The most prominent natural antagonist of biotin is above-mentioned avidin, a glycoprotein in raw egg white with a high affinity for biotin. Avidin binds biotin in a tight non-covalent complex preventing its absorption in the small intestine and thereby making it unavailable. The binding of biotin to avidin is the strongest known non-covalent bond in nature. The complex can neither be broken (i.e., to release biotin) because it is resistant to digestive proteases and is undissociated over a wide range of pH nor absorbed (i.e., as the intact complex molecule) in the intestine. Nutritionally, the binding phenomenon has however a little impact since heating to at least 100 °C during cooking denatures avidin, destroying the avidin-biotin complex and releasing the vitamin for absorption, as well as preventing additional complex formation. The consumption of raw or undercooked whole eggs is probably of little consequence for nutrition, as the biotin-binding capacity of avidin in the egg white is roughly comparable to the biotin content of the egg yolk. Similarly, raw egg white, if added to foods without further cooking or ingested with cooked food, provides avidin that binds the low amounts of biotin in food. Experimentally, it has been shown in humans that a diet containing 30 g of raw egg white per 100 g dry weight diet induces biotin deficiency [80, 393, 394, 396, 397, 405, 477, 478].

Effects of food processing on biotin content

Processing may influence the content of biotin in foods [134, 135, 163]. However, in contrast to other B vitamins, there is little available data on how food processing affects biotin content. An rough overview of data on biotin losses in some food groups due to processing is given in the Table S3 in Supplementary data. More data on specific foods, information on conditions, and comments are in the text below.

Milling and refining of cereals

Milling and refining cereal grains bring on a substantial decline in biotin due to removing grain parts rich in micronutrients.[144] Biotin amounts in refined wheat, rye, barley,

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and sorghum flours decrease, depending on the degree of milling, by 7–77%, 8–69%, 5–78%, and 7–72% in comparison to whole grain flours, resp. [144]. Likewise, the content of biotin in various maize milled products is reduced by 20–81% as compared to whole kernels [144, 146, 479]. Biotin losses in non-parboiled and parboiled white rice are 47–86% and 49%, resp., compared to brown rice [148, 149, 152, 480].

Properties of biotin and mechanisms of vitamin losses during food processing

Biotin is soluble in water and generally regarded as having good stability, being fairly stable to air (oxygen), light, and heat. It can, however, be gradually decomposed by ultraviolet radiation. Biotin is relatively stable in weak acid or alkaline solutions (pH 4 to 9), whereas it can be broken down in strong acid or alkaline solutions by heating [134, 135, 147, 154, 157, 163, 165, 394, 396, 481]. Losses of biotin during processing of foods are more related to leaching, although some thermal degradation may also occur [135, 481]. In contrast to other water-soluble vitamins, biotin is not so prone to leaching because it exists in foods at least partly in a protein-bound form, not enabling most likely leaching into cooking liquids [163, 396, 482].

Processing of animal-based foods

Biotin losses in pork, beef, chicken, and fish were estimated to be 20–30% during boiling, steaming, and braising, 15 % during frying, and only 10% during all cooking methods, if the vitamin content in soup, gravy, and drippings is taken into consideration (i.e., total dish) [170, 481]. Boiling, poaching, and frying of eggs lowered biotin content by 14%, 22% (higher losses owing to leaching into water), and 7%, resp.[185]. Boiling, pasteurization, ultra-heat treatment, and evaporation of milk do not substantially reduce biotin levels; losses are usually negligible, about 0–10% [163, 170, 481, 483].

Processing of plant-based foods

Estimated decreases in biotin content in vegetables are 30%, 15%, and 10% resp., due to boiling, steaming, and frying, and 10% if the cooking water is not discarded [170]. Therefore, steaming, compared to boiling, is associated with lower biotin loss. For example, boiling and steaming lessened biotin amounts in broccoli by 14.5% and 7.5%, resp. [188]. In legumes, mean biotin losses of 5% after cooking for 20 minutes and 5–12% after pre-soaking and cooking for 20–150 minutes occurred. Duration of pre-soaking (for 1 or 16 hours) did not

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affect biotin retention while cooking time did [484]. Biotin amounts in hazelnuts and walnuts decreased by 10% and 32%, resp., during baking [485]. Biotin losses of 10–25% during extrusion processing were reported [165].

Food preservation and storage

The contents of biotin were 40–77% lower in canned vegetables, such as carrots, tomato, spinach, corn, and green peas, compared to raw ones [152]. Ionizing radiation, which is used for food preservation, causes little or no loss of biotin; irradiation of wheat to 2 kGy gave a loss of 10% after 3 months storage [206].

Biotin in vacuum-packaged broccoli au gratin and almonds was stable during storage at room temperature either on the Earth or exposed to spaceflight for 880 days [209]. No change in the content of biotin in spray-dried milk powder happened during storage for 8 weeks at 60°C. At 70°C, the biotin level remained constant for the first 2 weeks of storage and then declined by 25% in the next 6 weeks. Biotin content in milk powder was unchanged after storage for 15 weeks in an oxygen or nitrogen atmosphere [486]. No biotin loss occurred in foods stored at -20°C or -80°C for 4 weeks [487].

Industrial production of biotin

Industrial production of biotin is currently based on chemical synthesis because its isolation from natural sources is not, due to very low concentrations, economically feasible. The majority of produced biotin is used in feed (about 90% of annual production [447, 488]; as a feed additive to prevent vitamin deficiency for animal health, welfare, and performance [447, 458, 488-511]), pharmaceutical, food (for dietary supplements and food fortification) [447, 488, 508, 512-518], and cosmetic industries [488, 519-521]. Only a minor portion is used for analytical purposes in the context of the biotin-avidin/streptavidin technology [488, 507, 522-529].

The molecule of biotin possesses three asymmetric centres giving rise to eight possible stereoisomers. Only one, D-(+)-biotin, has biological activity of the vitamin. Biotin manufacturing makes use of costly stereoselective multistep chemical synthesis, which was first achieved in the late 1940s and since then has still been improved. Alternative syntheses have also been investigated and developed [220, 221, 393, 447, 488, 507, 530-534]. The production of biotin by fermentation has attracted for a long time considerable interest from researchers due to economic and environmental sustainability concerns of the chemical process. Random

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mutagenesis and selection, as well as genetic engineering, have been used to remove metabolic obstacles and bottlenecks for obtaining biotin high producing microbial strains. However, to be cost-effective, it is assumed that any commercial bioprocess requires microbial strains that produce significantly more than 1 g biotin per liter in 12-24 hours of fermentation and use a cheap substrate. Overproducing strains of some bacteria have been developed, e.g., *Serratia marcescens*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas mutabilis*, *Bacillus sphaericus*, *Agrobacterium*/*Rhizobium* HK94, and *Sphingomonas* sp., the three first species being the best producers. Although the biotin yields achieved have already been close to the required level in some cases, none of the strains has really produced enough biotin to allow profitable production yet [225-227, 412, 427, 447, 508, 535-553]. In 2022, a Danish biotech company, Biosyntia, announced the intention to commercialize the first biotin produced by sustainable fermentation using genetically modified microorganisms. Biosyntia will, jointly with a German company, Wacker Group, develop a large-scale industrial bioprocess based on its proprietary technology [554]. The upcoming years will show whether the fermentative process is sufficiently efficient to be economically competitive with the currently used chemical one for biotin manufacturing.

Food fortification and biofortification with biotin

Regarding food fortification with biotin, the need is low because dietary biotin deficiency is rare [395, 447, 458, 460]. Biotin may be added to foods voluntarily by food manufacturers, e.g., to processed cereal-based foods for infants and young children, milk powders, rice powders, and breakfast cereals [214, 258, 259, 395, 508, 518, 555]. The biotin content of infant and follow-on formulae, and of processed ceral-based foods and baby foods for infants and children is regulated [214, 259]. As for the biofortification of crops with biotin, no attempt has been reported.

PHARMACOKINETICS OF BIOTIN

Absorption

Biotin is present in its free and protein-bound forms in foodstuffs. After being ingested, protein-bound forms of biotin are cleaved by gastrointestinal proteases and peptidases, giving origin to biocytin and biotin-oligopeptides [556, 557]. After that, biocytin and biotin-

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oligopeptides are hydrolysed by the enzyme biotinidase to release free biotin in the intestinal lumen. This enzyme is present in pancreatic juice, secretions of intestinal glands, bacterial microflora and the brush-border membranes [558]. The last hydrolytic step is considered to be crucial and influences the bioavailability of biotin (Figure 3) [556, 558].

Free biotin is then absorbed in the small intestine via a Na^+-dependent, carrier-mediated mechanism. The responsible transporter is expressed in the apical membrane of enterocytes [403, 559, 560]. This uptake mechanism seems to be the rate-limiting step of the biotin absorption, and the inwardly directed Na^+ gradient provides the energy for the transport [561]. The transporter is called sodium-dependent multivitamin transporter (SMVT) since it is also involved in the uptake of pantothenic acid (vitamin B_5) and lipoic acid [403, 562]. In addition to the apical membrane of intestinal cells, SMVT is also expressed in the liver, blood-brain barrier, heart, placenta and kidney [563-567]. The apparent Michaelis-Menten (K_m) constant of the transporter in rat jejunum was reported to be 3.7 μM [379]. The SMVT has 12 transmembrane domains, and it is encoded by the *SLC5A6* gene located on chromosome 2p23 [557, 568].

The transport from the enterocyte to the blood through the basolateral membrane is also carrier-mediated and Na^+-independent process whose identity is not yet known.

The absorption rate of the dietary biotin differs between portions of the intestine, being higher in the proximal (jejunum) compared to the distal part (ileum) of the small intestine [560]. In contrast, biotin produced by bacteria can be absorbed in the large intestine.

Humans are regulating biotin absorption in an adaptative mechanism according to the cell type. In intestinal epithelial cells, biotin deficiency is recognized by a deficiency-responsive region within the SMVT promoter. *Cis*-regulatory elements that bound the gut-enriched Kruppel-like factor (GKLF) were identified in this region. Briefly, in a biotin deficiency state, an increase in the promotor activity occurs by a transcriptional regulatory mechanism via GKLF, with induction in mRNA and protein levels of SMVT and subsequent up-regulation in biotin uptake.[569] On the contrary, in human liver cancer HepG2 cells, a biotin deficiency state causes a decrease in SMVT protein and mRNA levels, resulting in impaired biotin uptake [570].

It must also be mentioned that there are reports that biotin uptake in the intestine is not only mediated by SMVT. Bowman et al. reported intestinal biotin uptake to be mediated by both saturable and non-saturable components, with the saturable Na^+-dependent process occurring at lower concentrations [559, 571]. Similarly, studies in canine kidney cells revealed biotin

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uptake to be a two-component process. The major role played a saturable carrier-mediated process and a minor non-saturable component, which was evident at higher concentrations [567].

Distribution and metabolism

In plasma, biotin is primarily present in its free form (80%) and the remaining is bound to albumin, α-globulin, and β-globulin. Also, biotinidase can function as a biotin-carrier in plasma [572-574].

Intracellularly, biotin is localized mostly in the cytoplasm and mitochondria, where it exerts its role as a coenzyme for carboxylases. A small amount is also found in microsomes and nucleus [575, 576]. The liver contains the highest amount of biotin, and it is considered the major organ regarding biotin metabolism. Biotin uptake by human hepatocytes occurs again through SMVT [577].

Catabolism of biotin in mammals occurs *via* two pathways: a) β-oxidation of valeric acid side chain, which gives origin to bisnorbiotin, tetranorbiotin, and intermediates (α,β-dehydro-, β-hydroxy, and β-keto-intermediates) and b) oxidation of sulphur which produces biotin sulfoxide (Figure S2) [578]. Oxidation of sulphur moiety occurs probably in the endoplasmic reticulum and results in the formation of biotin-L-sulfoxide, biotin-D-sulfoxide, and biotin sulfone. NADP participates on this process [575]. Lastly, several compounds such as bisnorbiotin sulfone are produced as a result of β-oxidation and sulphur oxidation [578, 579]. Tetranorbiotin can be further degraded by microorganisms [580].

Excretion

Biotin and its metabolites undergo urinary and biliary excretion, with the former being the main excretion route. Studies in humans, rats, or pigs reported that 43-75% of the parenterally administered biotin dose is excreted into urine [474, 580]. Urinary excretion of biotin and its catabolites is approximately 100 nmol per day. Biotin accounts for approximately one half, the metabolites bisnorbiotin, biotin-D/L-sulfoxide, bisnorbiotin methyl ketone, biotin sulfone and tetranorbiotin-L-sulfoxide form the second half of the excreted amount [579]. Both renal and intestinal epithelial cells are involved in the regulation of biotin homeostasis. Urinary elimination of biotin is regulated *via* reabsorption of filtered

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biotin in the renal glomeruli and this process is again mediated by SMVT in the proximal tubular epithelial cells [581, 582].

PHYSIOLOGICAL FUNCTIONS OF BIOTIN

In humans, biotin plays a role as a coenzyme for carboxylases, influences chromatin structure and participates in gene regulation (Figure 4). Moreover, relatively recent studies have hypothesized additional roles in immunomodulation, inflammation and even cancer development.

Biotin-dependent carboxylases

Biotin undergoes several biological reactions that constitute the so-called biotin cycle (Figure 5A). Biotin cycle is important to maintain biotin levels inside the cell. After being absorbed in enterocytes, biotin holocarboxylase synthetase (HLCS) attaches biotin covalently to one of five biotin-dependent apocarboxylases.

This reaction is called biotinylation and it occurs according to the following two-steps:

1. ATP + biotin + HLCS → biotinyl–5'–AMP–HLCS + pyrophosphate
2. biotinyl–5'–AMP–HLCS + apocarboxylase → holocarboxylase + AMP + HLCS

The bond is formed between valeric acid side chain of biotin and a specific lysine residue in each carboxylase.[583] *In vitro* studies confirmed that the process of biotinylation of carboxylases is dependent on biotin concentrations [584, 585]. When needed, holocarboxylases are proteolysed to biocytin (i.e., biotin-lysine), which in turn releases free biotin by the action of the biotinidase. This process allows biotin to be recycled and maintain its homeostasis [378, 586].

Human cells have five biotin-dependent carboxylases with several roles and located in different cell compartments (Table 7 and Figure 5B) [475, 583]. The role of biotin is to transfer a carboxyl group from a donor to an acceptor biomolecule [587-589].

Biotinylation of histones

In contrast to the well-known participation of biotin in carboxylation, its role in gene transcription is a relatively new topic. The tail domain of histones is pivotal for several

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biological processes because modifications in this region influence chromatin, and hence processes such as gene regulation, chromosome condensation and DNA repair [590]. Biotinylation of histones, i.e., covalent attachment of biotin to the tail domain of histones is well documented [591, 592]. There is discussion about this process. Several hypotheses have arisen. According to Hymes *et al*, cleavage of biocytin (biotin-ε-lysine) by biotinidase leads to the formation of a biotinyl-thioester intermediate, and then the biotinyl moiety is transferred from the thioester to an ε-amino group of lysine of histones [593, 594]. Other studies indicated that biotin holocarboxylase synthetase can also biotinylate histones; indeed, they report that holocarboxylase synthetase is more important than biotinidase [595, 596]. Interestingly, some studies suggested that biotinidase may catalyse both biotinylation and debiotinylation of histones [597].

Investigation of the biological functions of histone biotinylation is still a wide-open field. Nevertheless, biotinylation of histones might be important in cellular response to DNA damage [598]. Biotinylation of the lysine K12 in histone H4 plays roles in gene repression, DNA repair, heterochromatin structures, and repression of transposons, thereby promoting genomic stability. Also, knockdown of biotinidase or holocarboxylase synthetase decreases life span and heat resistance in *Drosophila melanogaster*, probably suggesting that a decrease in histone biotinylation causes abnormal gene expression patterns [595].

Biotinylation of signalling molecules and transcription factors

Biotin also participates in the regulation of gene expression through various cell signals and transcription factors, such as biotinyl-AMP, cGMP, nuclear factor-κB, Sp1 and Sp3, and receptor tyrosine kinases [599]. Thousands of genes are affected by biotin, including genes involved in glucose homeostasis. One *in vitro* study showed that incubation during 48 h with 10 nM biotin increases pancreatic glucokinase activity in rat pancreatic islets primary cultures, and 100 nM biotin duplicated the activity observed in control. Also, glucokinase mRNA levels increased by ~80% after incubation with 1 μM biotin during 24 h [600]. Moreover, a study using rat hepatocytes demonstrated that the addition of biotin (1 μM) to the culture medium induces a 3-fold increase in the content of cGMP and a 4-fold increase in the glucokinase activity and its mRNA levels [601]. Thus, both pancreatic and hepatic glucokinase are regulated by biotin in a positive manner [600, 601].

Regarding the underlying mechanisms involved in gene regulation, biotinyl-AMP, which is the intermediary product formed by the action of holocarboxylase synthetase, is

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thought to be responsible for the gene regulatory functions of biotin. Biotinyl-AMP activates the soluble guanylate cyclase with a subsequent increase in intracellular concentration of cGMP and activation of protein kinase G [602, 603]. This signal transduction pathway is involved in the regulation of genes involved in biotin homeostasis and function, including biotin-dependent carboxylases and holocarboxylase synthetase, SMVT, but also others (e.g. asialoglycoprotein receptor, oncogenes). Holocarboxylase synthetase mRNA levels in the liver, kidney, muscle, and brain of rats fed a biotin-deficient diet were significantly lower compared to the controls. On the other hand, pyruvate and propionyl CoA carboxylase mRNA levels were not altered, while the amounts of these enzymes were lower.[604] Biotin was also identified as the factor required for the expression of asialoglycoprotein receptor in a human liver cancer cell line HepG2 [605]. Moreover, *in vitro* studies demonstrated that expression of oncogenes N-myc, c-myb, N-ras, and raf correlate positively with biotin concentrations. A pharmacological concentration of biotin (10 nM) increased the expression of N-myc to 120%, whereas a very low biotin concentration (25 pM) decreased it to 53% compared to the controls containing biotin at a physiological concentration (250 pM) [606]. Moreover, some studies indicate that biotin-dependent genes are clustered in specific chromosomes [607].

Biotin as anti-inflammatory and immunomodulator

Recent studies also reported a link between biotin and immune and inflammatory functions. Mice not-absorbing biotin due to knockout in SMVT gene revealed chronic inflammation in the cecum [608]. Biotin-deficient human monocyte-derived dendritic cells demonstrated a higher secretion of cytokines such as TNF-α (tumour necrosis factor α), IL-12p40, IL-23, and IL-1β [609]. Biotinidase deficiency, an inborn disorder characterized by impaired biotin bioavailability and recycling, can be associated with weakened immunity manifested by recurrent infections and dermatitis [610]. Indeed, biotin deficiencies are often associated with skin manifestations [611]. The underlying pathophysiological mechanisms could be alterations in the role of biotin-dependent carboxylases, such as acetyl-CoA carboxylase 1 or propionyl-CoA carboxylase, hence interfering with fatty acid metabolism and the cutaneous immune system. Moreover, immune and inflammatory functions of biotin cannot be explained solely by the involvement in carboxylation but also via its effects on transcriptional factors such as nuclear factor κB and Sp1/3 [599]. Nuclear factor κB regulates genes involved in inflammation

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and innate and adaptive immune response. Sp1 and Sp3 have been associated with the expression of the gene encoding cytokine IL-10 [612].

LABORATORY ASSESSMENT OF BIOTIN STATUS

Methods for measurement of biotin are summarized in Table 2 (more details are shown in Supplementary Data Table S2). Indicators of biotin status could be helpful in the diagnosis of conditions associated with biotin deficiency. Stratton et al. identified lymphocyte propionyl-CoA carboxylase (PCC) activity as an indicator of biotin deficiency in humans [613]. However, due to analytical issues, PCC assay is not adequate to assess biotin status in large population studies. Another marker is the plasma level of 3-hydroxyisovaleryl carnitine. This might be an early and sensitive indicator of biotin deficiency in humans [614]. Moreover, urinary 3-hydroxyisovaleryl carnitine might also be used [615].

BIOTIN DEFICIENCY AND RELATED DISORDERS

Frank biotin deficiency cases were reported in people who consume raw egg white for long periods, in cases of parenteral nutrition, and inborn errors of metabolism that cause biotin wasting [379, 616].

Nutritional biotin deficiency and inherited disorders associated with gene mutations encoding holocarboxylase synthetase or biotinidase give origin to a pathological state called multiple carboxylase deficiency. The pathophysiological mechanisms include: 1) in the case of holocarboxylase synthetase deficiency, a decrease in the affinity of holocarboxylase synthetase for biotin with consequent impairment in the formation of holocarboxylases at physiological biotin levels and 2) in the case of biotinidase deficiency, alterations in biotin release from its protein conjugates and hence its recycling (Figure 5A). This is followed by its loss in urine as biocytin. The estimated incidence of biotinidase deficiency is ~ 1:60,000–80,000 of new-borns, whereas holocarboxylase synthetase deficiency is estimated to be less than 1:200,000 of new-borns. Both are autosomal recessive disorders. Clinical manifestations of biotinidase deficiency include seizures, hypotonia, lack of coordinated movement and balance impairment, respiratory problems, hearing and vision loss, skin rashes, hair loss and retarded cognitive and physical development. Holocarboxylase synthetase deficiency symptoms include severe metabolic acidosis, lethargy, hypotonia, vomiting, seizures, hypothermia, and unconsciousness, and even coma and death. All these clinical

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manifestations from both disorders respond well to early treatment through biotin supplementation [617]. The dose needed for the treatment is not excessive, and the onset of the effect is relatively rapid. In a case report of 2 Chinese infants with late-onset holocarboxylases synthetase deficiency, 30 mg/day biotin treatment in the initial phase solved the metabolic disorders within 48 hours. Moreover, in the following period, biotin supplementation improved the patient clinical conditions [618].

Biotin-thiamine-responsive basal ganglia disease is a rare autosomal recessive neurometabolic disorder. Formerly, it was called biotin-responsive basal ganglia disease and described as a subacute encephalopathy, with confusion, dysarthria, and dysphagia with occasional supranuclear facial nerve palsy or external ophthalmoplegia that can progress to severe quadriparesis and even death. Symptoms of biotin-thiamine-responsive basal ganglia disease disappear within a few days with biotin treatment (5-10 mg/kg/day), and relapse occurs within one month if biotin is discontinued [619]. Recent studies have shown that regimens for curing this condition shall include both biotin and thiamine to treat and prevent acute crises and relapses [620].

Recent clinical studies have focused on cases of marginal biotin deficiency. Their incidence is higher than was assumed in the past [615]. Logically, the absence of symptoms commonly present in biotin deficiency is not a suitable marker for vitamin B_7 marginal deficiency.

Biotin deficiency is teratogenic in several animal species. In mice, egg-induced biotin deficiency caused a higher incidence of cranial malformations and shortening of the long limb bones [621]. It need not be emphasized that other vitamins of the B complex, like folic acid, have already been shown to be essential [622]. Hence, the role and kinetic of biotin in pregnancy deserve attention. A cross-sectional study of normal human gestation reported an increased excretion of 3-hydroxyisovaleric acid in early and late pregnancy. However, there was a paradoxical increase in biotin excretion late in pregnancy, suggesting that biotin status in pregnancy was not reduced [623]. On the other hand, a longitudinal study with women from early to late pregnancy evidenced that biotin status decreases during pregnancy. By late pregnancy, approximately half of the participants showed less than the lower limit of normal biotin excretion rates [624].

PHARMACOLOGICAL USE OF BIOTIN

Pharmacologic doses of biotin are used for treating patients with disorders of biotin metabolism as mentioned in the previous chapter. Holocarboxylase synthetase deficiency can

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be treated with 10 mg biotin/day with children showing improvement in their condition, while biotinidase deficiency can be treated with a dose of 5–20 mg biotin daily [380].

Considering the potential neuroprotective role of biotin, its use in the treatment of neurological diseases could be beneficial. In an open-label study with 23 patients with primary and secondary progressive multiple sclerosis, treatment with high-dose biotin (100–300 mg/day) from 2 to 36 months revealed an improvement in several symptoms. Overall, the clinical improvement was delayed by 2–8 months, and 300 mg biotin/day, a 10 000 times higher dose than the recommended daily intake, generated the best clinical response [625]. Some mechanisms were suggested to be responsible: 1) activation of pyruvate carboxylase, propionyl-CoA carboxylase and methylcrotonyl-CoA carboxylase may lead to an increase in ATP production in neurons and 2) activation of acetyl-CoA carboxylases may lead to myelin repair.[625] A double-blind, placebo-controlled study with 154 patients with primary or secondary progressive multiple sclerosis receiving 100 mg of biotin orally, thrice daily or placebo for 12 months corroborated the previous findings [626]. In contrast, in an observational prospective study of 178 patients again with primary and secondary progressive multiple sclerosis, high-dose biotin did not show a clear improvement in disability and quality of life [627].

Regarding dietary biotin supplements, they frequently appear as combinations of the B-complex vitamins or multivitamin complexes. Its main indications are to fortify hair, nails and skin. Although several reports have evidenced clinical improvement after biotin supplementation in cases of biotin deficiency, research demonstrating its efficacy in hair and nail growth in healthy individuals is limited [628].

Biotin is synthesized *de novo* in plants, fungi and microorganisms, and this property might be used from a therapeutic point of view. For instance, *Mycobacterium tuberculosis* needs to biosynthesize this vitamin for its pathogenicity during all stages of the life cycle. For this reason, inhibitors of biotin biosynthetic enzymes could be a potential target for the development of novel antibiotics against tuberculosis [629].

TOXICITY OF BIOTIN

Due to being water-soluble, excessive amounts of biotin are known to be easily excreted. Hence, it seems this vitamin is relatively nontoxic. Moreover, the maximum daily dose unlikely to cause adverse side effects in the general population, i.e., tolerable upper intake level, has not yet been established [630, 631].

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Regardless, there are some concerns about high-dose biotin. A case report of a 54-year-old woman with progressive multiple sclerosis reported an aggravation of the neurologic state, accompanied by lipid storage in muscle, after five months of treatment with three times 100 mg biotin per day. Symptoms disappeared in a few months after biotin withdrawal [632]. In addition, animal experiments with mice fed with a biotin-supplemented diet (97.7 mg free biotin/kg) over 8 weeks revealed alterations in the testis [633]. In addition, experiments with rats fed 5000 and 8000 mg biotin/kg diets for 28 days showed a decrease in testis weight [634]. These results are in disagreement with *in vitro* fertilization studies in which biotin supplementation to sperm wash medium (2.44 mg/mL) improved fertilizing ability of mice spermatozoa [635].

INTERFERENCES WITH TESTS

Elevated blood levels of biotin cause interference in streptavidin-biotin hormone immunoassays [636-638]. In competitive assays (e.g. triiodothyronine, thyroxine, steroid hormones, 25-hydroxyvitamin D), there are falsely increased hormones concentrations, whereas in sandwich assays (e.g. glycoprotein regulating hormones) falsely decreased hormones concentrations have been reported [639]. The degree of interference is dependent on plasma biotin concentration, and it is significant at concentrations of 30 µg/L or more [637]. False hyperthyroidism is the most frequently misdiagnosed endocrine disorder [514, 637, 640-642]. Likewise, false high 25-hydroxyvitamin D serum levels were detected in patients receiving high dose of biotin (> 100 mg). Logically, several concerns arise, since this is a crucial laboratory test in multiple sclerosis patients receiving vitamin D supplementation [637, 643, 644]. Biotin interference in cardiac troponin assays have also been reported [645, 646]. Although, one analysis using a Roche assay led to the conclusion that this interference is rare, and its probability is even lower than other confounders such as blood sample hemolysis and simple biological variation of cardiac troponin [647]. The International Federation for Clinical Chemistry Committee on Cardiac Biomarkers (IFCC-CB) reported a cardiac troponin assay interference table for hemolysis and biotin to guide healthcare professionals and clinicians whenever there is an inconsistency between cardiac biomarker results and the clinical situation [645].

Biotin supplementation has also been linked to alterations in hepatitis B-virus (HBV), hepatitis C-virus (HCV), and human immunodeficiency virus (HIV)-related serological markers [648]. A study in which 10 healthy volunteers vaccinated against hepatitis B were

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administered a single oral dose of biotin (100 mg) revealed anti-HBs levels below the cutoff value for four of the ten participants. Moreover, around 80 to 90% of false positive results for anti-HBe and anti-HBc occurred. On the contrary, in HIV and HCV serology testing, biotin caused false negative results [(648)].

CONCLUSIONS

The current review summarized the literature on two B-group vitamins B_6 and B_7 (also known as H or biotin). Historically, the research interest in these two water-soluble vitamins commenced at the beginning of the 20th century and allowed for the identification of numerous characteristics and essential roles in multiple physiological functions (e.g., neurological and metabolic processes). Novel discoveries, however, revealed their much larger physiological roles beyond their participation in multiple enzymatic reactions. Humans lack biosynthetic pathways of vitamins B_6 and B_7 and, therefore, must obtain them from exogenous sources (e.g., foods and supplements). These vitamins are also synthesized by the microbiota in the human large intestine and likely part of such produced vitamin, at least in the case of biotin, can be absorbed and used by humans. Cases of deficiency of vitamins B_6 and B_7 are rare. However, inherited disorders associated with gene mutations require prompt and lifelong treatment with these vitamins, starting at early life stages (i.e., in newborns). Moreover, vitamin B_6 lack can follow administration of several clinically used drugs (e.g. isoniazid) or poisoning with *Gyromitra* mushroom and *Ginkgo biloba* seeds. Beyond, cases of lack, both vitamins have been used or tested in several other conditions. For instance, pyridoxine has been used for prevention of vomiting in pregnancy while biotin, has been recently tested in controlled trials with patients with primary and secondary progressive multiple sclerosis. Last but not least, both vitamins are considered relatively non-toxic whether an adequate intake is followed.

Recent research has brought novel discoveries linking both vitamin B_6 and biotin with anti-inflammatory effects in particular. However therapeutic use of both vitamins in various inflammatory disorders still needs much larger research. In the case of biotin, further investigation of its role in gene expression regulation through both transcription factors and epigenetic processes is necessary.

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contributed to critical assessment of the paper, N.P., L.K.K. and L.K. prepared and critically assessed chemical and analytical issues, P.M. was responsible for conceptualization, critical view, finalization and obtained funding for the open access publication. All authors participated in the critical revision of the article.

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Figure S1. Biotin content of selected foods determined by different methods.

Figure S2. Pathways of catabolic reactions of biotin.

Table S1. A rough overview of data on vitamin B6 losses in some food groups due to processing.

Table S2. Detailed summary analytical methods for the assessment of vitamins B_6 and B_7 in biological fluids.

Table S3. A rough overview of data on vitamin B_7 losses in some food groups due to processing.

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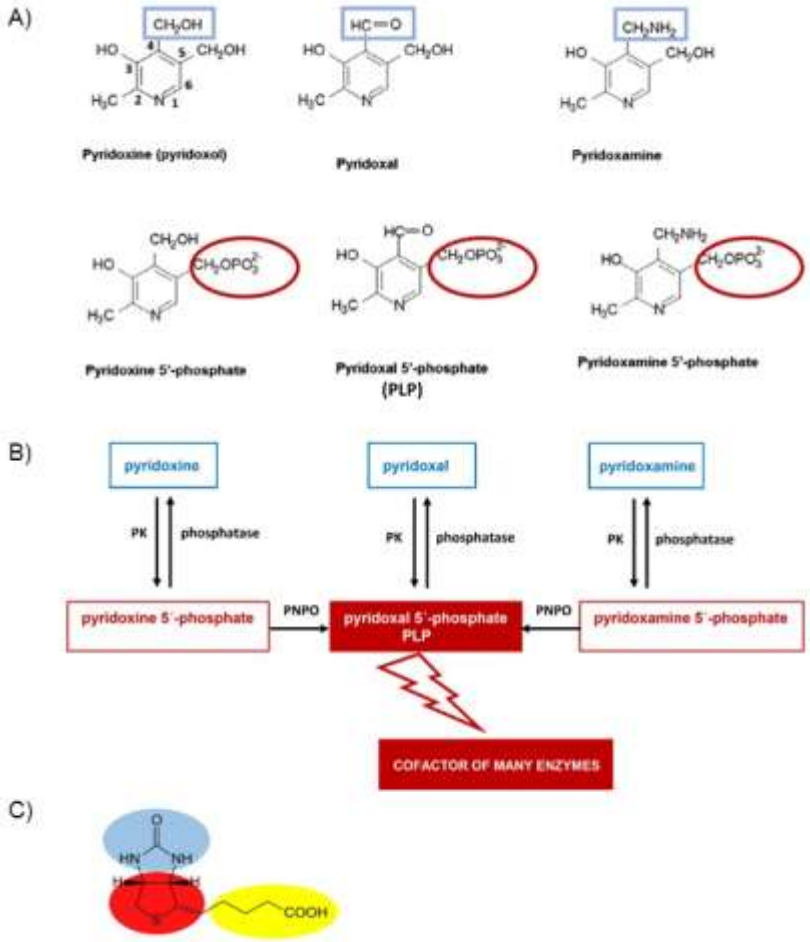

Figure 1. Chemical structures of vitamin $B_{6,}$ including its active forms, and vitamin B_7. A) Structure of the vitamers of B_6. B) Vitamin B_6 salvage pathway. PK–pyridoxine/pyridoxamine/pyridoxal kinase; PNPO–pyridoxine phosphate oxidase. C) Chemical structure of D(+)-biotin. Biotin molecule is composed of two rings: imidazolidinone ring (blue) and a tetrahydrothiophene group (red) attached to a valeric acid moiety as a side chain (yellow).

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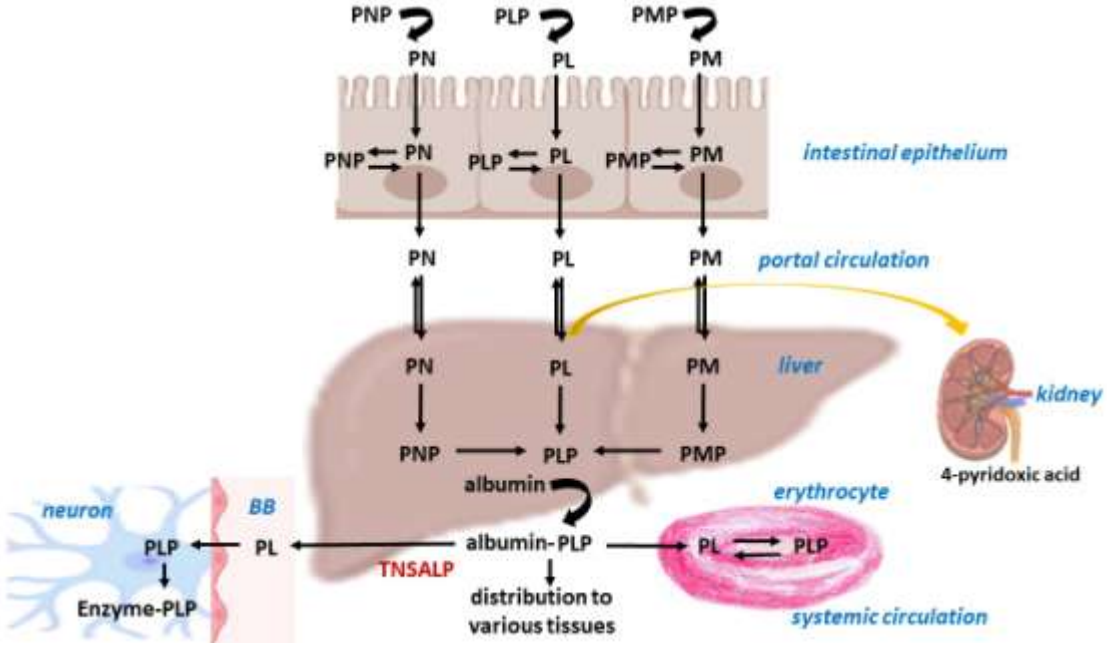

Figure 2. Pharmacokinetics of vitamin B_6. The figure summarizes pharmacokinetic of vitamin B_6 in the human body. PN – pyridoxine; PNP – pyridoxine 5'-phosphate; PL – pyridoxal; PLP – pyridoxal 5'-phosphate; PM – pyridoxamine; PMP – pyridoxamine 5'-phosphate; TNSALP – tissue non-specific alkaline phosphatase; BB – blood-brain barrier.

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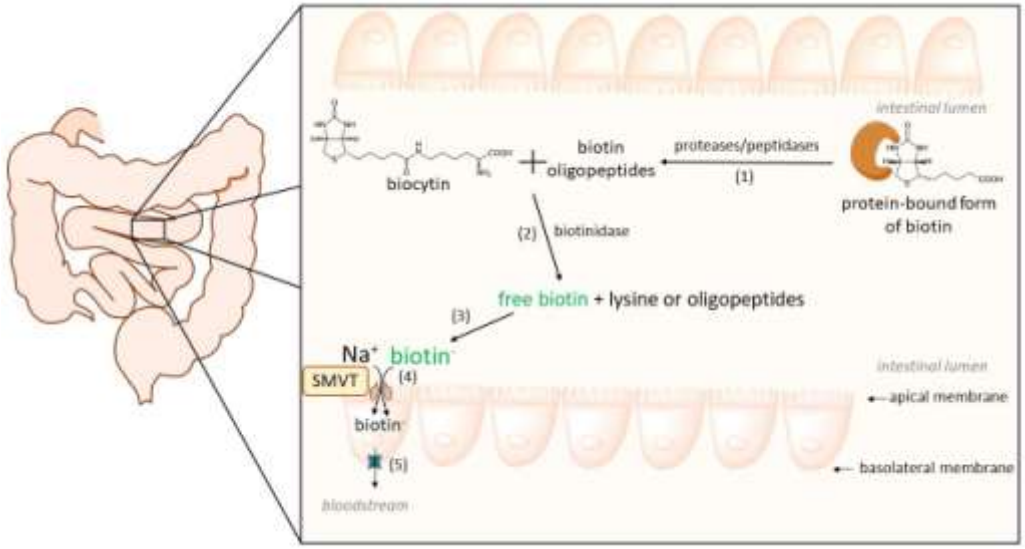

Figure 3. Human intestinal absorption of dietary biotin. Firstly, protein-bound forms of biotin are cleaved by gastrointestinal proteases/peptidases (1); then, biocytin and biotin-oligopeptides are hydrolysed by biotinidase (2) to release free biotin (3). Biotin enters enterocytes at the apical membrane through a saturable and Na^+-dependent carrier-mediated process (4) by sodium-dependent multivitamin transporter (SMVT). The identity of the basolateral transporter is not yet known (5, shown in blue).

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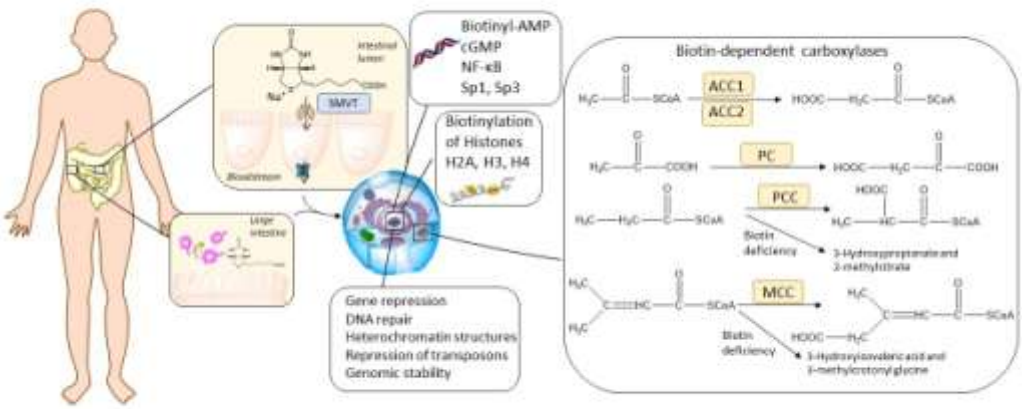

Figure 4. Summary of physiological functions of vitamin B_7 (a more detailed description is included in the corresponding sections of the article).

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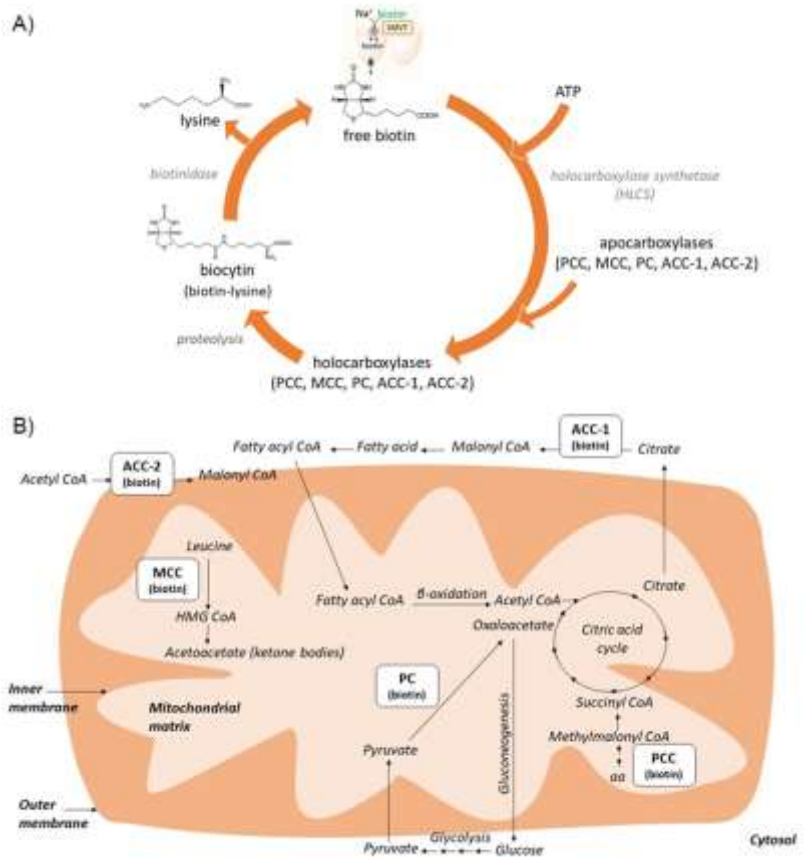

Figure 5. Physiological function of biotin. A) Schematic representation of the biotin cycle. Free biotin binds covalently to 5 apocarboxylases: propionyl-CoA carboxylase (PCC), methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), acetyl-CoA carboxylases (ACC-1 and ACC-2), by the action of biotin holocarboxylase synthetase. This step requires ATP and gives origin to active holocarboxylases, which are important in amino acid catabolism, synthesis and oxidation of fatty acids and gluconeogenesis. When needed, holocarboxylases can be proteolysed to biocytin. Then, biotinidase allows the release of free biotin. Adapted from [378, 586]. B) Simplified scheme of a human mitochondrion and biotin-dependent carboxylases, their role and location (cytosol, outer membrane, and matrix). ACC-1 – acetyl-CoA carboxylase 1; ACC-2 – acetyl-CoA carboxylase 2; PCC – propionyl-CoA carboxylase; MCC – methylcrotonyl-CoA carboxylase; PC – pyruvate carboxylase; aa – amino acids (valine, isoleucine, methionine, threonine). Adapted from **[649]**.

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Table 1. Vitamin B_6 content in selected foodstuffs.

Food	Vitamin B_6 content (µg/100 g)	References
Oat	120–960	(47, 650, 651)
Wheat	127–407	(45, 47, 138, 139, 142, 190, 203, 272, 650-652)
Rice, brown	123–563	(142, 143, 148, 149)
Rice, white	93–161	(142, 143, 148, 149)
Maize	307–620	(47, 142, 145, 650, 651)
Rye	202–290	(47, 138, 650, 651)
Barley	231–1100	(47, 138, 650, 651)
Millet	380	(650)
Sorghum	170-590	(653)
Soybean	267–550	(80, 654, 655)
Lentil	540	(476)
Peanut	260–350	(654, 656, 657)
Macadamia nut	218–300	(196, 658)
Pistachio nut	1032–1700	(47, 196, 654, 658)
Hazelnut	378–600	(47, 196, 658)
Walnut	443–540	(47, 196, 654, 658)
Almond	100–188	(80, 196, 654, 658-661)
Garlic	1240	(476)
Potato	140–345	(47, 142, 188)
Carrot	60–206	(47, 80, 188)
Cabbage	65–140	(47, 188)
Tomato	60–65	(47, 188)
Broccoli	130–190	(47, 188)
Cauliflower	140–170	(47, 188)
Spinach	120–227	(47, 188)
Orange	83–88	(47, 80)
Avocado	290	(662)
Strawberry	30	(47, 188)
Apple	56–104	(47, 80, 188)
Pear	14–40	(47, 188)
White bread	16–80	(80, 143, 190, 663, 664)
Brown bread	79–170	(80, 143, 190, 663, 664)
Pork	370–540	(31, 39, 142, 476, 665)

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Beef	264–579	(31, 38, 39, 142, 476)
Chicken breast	330–811	(476, 666, 667)
Liver, beef	840–1080	(39, 476)
Liver, pork	690	(39, 476)
Tuna	430	(668)
Sardines	310	(668)
Baker's yeasts	430	(476)
Oyster mushroom	100–110	(476, 669)
Button mushroom	50–77	(208, 476, 669)

(continued)

Food	**Vitamin B_6 content (µg/100 g)**	**References**
Milk	35–60	(48, 142, 467, 670)
Youghurt	87–100	(467, 670)
Cheese, cheddar	69	(476)
Eggs	130–241	(48, 142, 185)

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Table 2. Summary of analytical methods for the assessment of vitamins B_6 and B_7 in biological fluids.

Technique	Sensitivity (nmol/L)	Analytes	Matrix	Advantages	Disadvantages	Ref.	Publication year
LC-MS	0.1 – 127.51 x 10^3	B_6, B_6-PL, B_6-P5P, B_6-PM, B_7, B_6-PA, $B_{6,7,9}$ and its vitamers, metabolites and others	* human milk * serum * whole blood * plasma * mice brain samples * tears * faeces	Usually short analysis time, small sample volume (30 - 250 µL), using MRM in detection, simple methods for various matrices	Some methods have complicated sample preparation (breast milk) and complicated gradient elution, some methods use SIM and are not fully validated.	(671)-353	2012-2024
HPLC-FLD	0.3 – 20	B_6-P5P, B_6-PL, B_6-PA and others	* whole blood * cerebrospinal fluid * serum	Methods use small sample volume (100 -250 µL) and some of them simple derivatization procedure.	Methods have no IS included, usually complicated sample preparation, long analysis time with post column derivatization.	(672)-357	2004-2020
HPLC-PDA ***2D-LC-UV***	0.1 – 7.29 x 10^3	B_6, B_6-PL, B_6-P5P, B_6-PA and others	* urine * plasma * animal plasma	Methods use small sample volume (60 µL).	Methods haven't optimal recovery, there is long analysis time, poor sensitivity, derivatization, complicated sample preparation, and no IS.	(673)-359	2014-2023
MLC-PDA	0.177 × 10^3	B_6	* plasma	Method has simple sample preparation	No IS is used.	(674)	2021

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							(continued)
Sensors / nanodots / CL / FLD / ECD	5 – 9.06 x 10^3	B_6, B_6-PL, B_7, and others	* serum * urine * plasma * whole blood * artificial urine	Usually simple sample preparation, small sample volume (10 µL) and small solvents consumption, low price, some methods use common screen-printed carbon electrode	Standard addition method is not suitable in clinical analysis, necessity of electrode, nanocomposite or carbon nanosheet preparation, technique is research only - not commercially available, electrodes are prepared in laboratory, higher detection limits compared to modified electrodes, some methods use large sample volumes (10 mL)	(675)-370	2018-2023
Microbiological test kits	2.87 - 14.57	B_6-P5P B_7	* serum	Small sample volume (50 µL)	High price (working in duplicate recommended), usually long analysis time (24 h), ATBs in patients' sample could influence results	(676)-372	
HPLC-FLD kits	1.62 – 4.21	B_6-P5P, and others	* plasma * whole blood * serum	Small sample volume (100 – 300 µL)	No IS is used, long analysis time, different extraction procedures for each vitamin, different analysis conditions (temperature etc.), high price for small sample series	(677)-374	2021
							(continued)
LC-MS/MS kits	1.5 – 6.96	B_6-PL, B_6-P5P,	* whole blood		High price for small sample	(678)	2021

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		and others		Methods use IS, MRM, there is short analysis time, small sample volume (50 µL) combined with simple sample preparation	series	
ELISA kits	0.13 - 51.16 × 10^{-3}	B_7	* serum * plasma * urine	Methods use small sample volume (50 - 250 µL). One kit is suitable for various matrices, high sensitivity	Methods are for research only, cross reactivity with analogues, time consuming methods with high price for small sample series	(679)-377 2021

B6 pyridoxine; B6-PL pyridoxal; B6-P5P pyridoxal-5-phosphate; B6-PM pyridoxamine; B6-PA pyridoxic acid; B7 biotin; B9 folic acid; B9-THF tetrahydrofolic acid; B12 cyanocobalamin;

ATB Antibiotic; CL Chemiluminescence; ECD Electrochemical Detection; ELISA Enzyme-Linked ImmunoSorbent Assay; FLD Fluorescence Detection; HPLC High Performance Liquid Chromatography; IS Internal Standard; LC-MS Coupling of Liquid Chromatography and Mass Spectrometry; MLC Micellar Liquid Chromatography; MRM Multiple Reaction Monitoring; MS Mass Spectrometer; MS/MS Tandem Mass Spectrometry; PDA PhotoDiode Array Detection; SIM Selected Ion Monitoring; 2D-LC Two-dimensional Liquid Chromatography

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Table 3. Inborn metabolic disorders related to pyridoxine dependent seizures.

Disease (synonyms)	Genetic defect	Other symptoms except seizures
Antiquitin deficiency (Pyridoxine-dependent seizures)	ALDH7A1	developmental delay, intellectual disability, abdominal distention
Hyperprolinaemia II (Pyrroline Carboxylate Dehydrogenase Deficiency)	ALDH4A1	developmental delay, mental retardation
PNPO deficiency (Pyridoxamine5´-phosphate oxidase deficiency)	PNPO	developmental delay, sideroblastic anaemia, microcephaly, feeding difficulties
PLPBP deficiency	PLPBP	developmental delay, intellectual disability, microcephaly, anaemia
Hypophosphatasia	ALPL	impaired calcification of bones/teeth, anaemia, respiratory insufficiency
Hyperphosphatasia (Mabry syndome)	PIGV, PIGO, PGAP2	mental retardation, intellectual disability, facial dysmorphism brachytelephalangy anal stenosis

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Table 4. Recommendations for vitamin B_6 intake by gender and age.[286]

Individuals	Condition, age	Dose (mg/day)
Men	19-50 years	1.3
	> 51 years	1.7
Women	19-50 years	1.3
	> 51 years	1.5
	pregnancy	1.9
	lactation	2.0
Children	up to 6 months	0.1
	7-11 months	0.3
	1-3 years	0.5
	4-8 years	0.6
	9-13 years	1.0
Adolescent male	14-18 years	1.3
Adolescent female	14-18 years	1.2

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Table 5. Adequate intake level of biotin by life stage according to WHO and EFSA.

	WHO - AI levels (µg/day)		**EFSA - AI levels (µg/day)**
Infants and children		**Infants and children**	
0–6 months	5	–	–
7–12 months	6	7–11 months	6
1–3 years	8	1-3 years	20
4–6 years	12	4–6 years	25
7–9 years	20	7–10 years	25
Adolescents		**Adolescents**	
10–18 years	25	11–14 years	35
		15–17 years	35
Adults, 19+ years		**Adults, 18+ years**	
Females*/Males	30	Females*/Males	40
Lactating women	35	**Lactating women**	45

*including pregnant women; data are from[389, 390]; AI levels – adequate intake level, EFSA – European Food Safety Authority; WHO – World Health Organization.

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Table 6. Biotin content in selected foodstuffs.

Food	Biotin content (µg/100 g)	References
Oat	13–21.7	(466, 680, 681)
Wheat	8.3–11.6	(144, 680-682)
Rice, brown	4.2–12	(144, 471, 680, 681)
Rice, white	1.1–3	(471, 681)
Maize	6–8.3	(144, 146, 680-682)
Rye	5–14.5	(144, 680, 681)
Barley	10–20.5	(144, 461, 681)
Millet	4.6–14.4	(680, 683)
Sorghum	15.4–33.3	(144, 461, 680, 682)
Soybean	21.9–60	(397, 461, 466, 484, 655, 680)
Lentil	17.4–23.1	(484, 680)
Peanut, roasted, salted	34–82	(399, 461, 463, 466, 681)
Macadamia nut, roasted, salted	6–6.5	(471, 680)
Pistachio nut, roasted, salted	16.4–32	(463, 681)
Hazelnut	61.6–76	(397, 471, 681)
Walnut	17.3–35.5	(397, 461, 463, 681)
Almond	32.9–64	(209, 463, 466, 471)
Garlic	1.5–2	(463, 680, 681)
Potato	0.3–0.4	(188, 680)
Carrot	0.3–2.8	(188, 463, 466, 680)
Cabbage	0.8–2.2	(463, 466, 680)
Tomato	0.7–3.6	(188, 387, 463, 466, 680)
Broccoli	1.9–6.5	(188, 463, 466)
Cauliflower	1.7–10	(188, 463, 466, 680)
Spinach	2.9–4	(463, 466, 680)
Orange	1–2	(188, 681)
Avocado	1–4.3	(387, 466, 471)
Strawberry	0.8–2.2	(188, 387, 466, 680)
Apple	0.7–1.6	(188, 466, 680, 681)
Pear	0.3	(188, 680)
White bread	0.6–1.6	(466, 471)
Brown bread	3	(471)
Pork	1.5–5	(39, 387, 466)

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Beef	1.2–3	(39, 461, 466)
Chicken breast	2.4–3.2	(466, 680)
Liver, beef	41.6–76.1	(387, 466, 680)
Liver, pork	54.5–79.6	(466, 680)
Tuna	1.2–2.8	(466, 668, 680)
Sardines	7.2–18.3	(466, 668, 680)
Baker’s yeasts	20.2–80	(387, 461, 471)
Oyster mushroom	12	(680)
Button mushroom	10.6–24.4	(469, 680, 681)
Milk	1.4–4.3	(179, 397, 461, 466, 670, 680, 681, 684, 685)
Yoghurt	0.9–4	(466, 467, 471, 670, 680, 681, 684)
Cheese, cheddar	1.4–3.8	(387, 462, 466, 471, 680, 681)
Eggs	19.5–25.4	(185, 387, 397, 399, 461, 466, 680, 681)

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Table 7. Biotin-dependent carboxylases, their location in cells and roles.

Biotin-dependent carboxylases	Location	Roles	References
Acetyl-CoA carboxylase 1 (ACC-1)	Cytosol	Carboxylation of acetyl-CoA to malonyl-CoA. ACC-1 isoform is expressed in lipogenic tissues such as the liver and kidney.	(686)
Acetyl-CoA carboxylase 2 (ACC-2)	Outer mitochondrial membrane	Carboxylation of acetyl-CoA to malonyl-CoA. ACC-2 isoform is expressed in skeletal muscles and the heart, tissues where fatty acid oxidation is important.	(686)
Methylcrotonyl-CoA carboxylase (MCC)	Mitochondrial matrix	Catabolism of leucine and carboxylation of 3-methylcrotonyl-CoA to 3-methylglutaconyl-CoA.	(687)
Pyruvate carboxylase (PC)	Mitochondrial matrix	Catalysis of the transformation of pyruvate to oxaloacetate.	(688)
Propionyl-CoA carboxylase (PCC)	Mitochondrial matrix	Catalysis of the conversion of propionyl-CoA to methylmalonyl-CoA.	(689)

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