Vitamins basics

Everything you need to know about vitamins for health and wellbeing
Introducing DSM’s Scientific Services

Science-based expertise supporting innovations that meet consumer needs

DSM’s Scientific Services provide expert support around life sciences, in particular nutrition sciences, tailored to innovations and target consumers. We elaborate the scientific substantiation to meet the requirements of different stakeholder groups, including academia, the scientific community, regulatory experts, health care professionals and consumers. Our science-led advice enables our customers to create and market nutritional solutions based on health benefit acumen.

This document explores the significance of vitamins in supporting our health and wellbeing and offers an in-depth guide to the functions that all 13 individual vitamins have in the body.
Why are vitamins important?

Vitamins are essential nutrients that are required by humans in small amounts. This is why they are known as micronutrients. Vitamins are vital for life, aiding normal growth and healthy bodily functions such as cardiovascular, cognitive and eye health.

They are needed for processes that create or use energy, such as the metabolism of proteins and fats, the digestion of food and absorption of nutrients, growth and development, physical performance, and regulation of cell function, with each vitamin having important and specific functions within the body. Aside from vitamin D3, vitamins are not produced by the human body and must therefore be obtained via the diet.

Where do vitamins fit into our diets?

Being complex organisms, humans have a host of nutritional needs. In order to maintain healthy lives, it is vital that we consume the correct nutrients through our diet to maintain normal body function. The different types of nutrients that we need can be split into two categories: macronutrients (carbohydrates, proteins and fats) and micronutrients (vitamins and minerals) (figure 1). While micronutrients, such as vitamins, are not required in the same quantities as macronutrients, they are equally as important for our bodies, as both work together to maintain overall health.

Vitamins can be further categorized into fat-soluble and water-soluble types. Fat-soluble vitamins, including vitamins A, D, E and K, are stored in the body’s fat tissue which acts as a resource of fat-soluble vitamins if they are not consumed every day. The remaining nine vitamins are water-soluble and must be used by the body immediately once consumed. The exception is vitamin B12, which can be stored in the liver for many years.
Successfully bridging nutritional gaps

Approximately one-third of the global population has a suboptimal micronutrient status as a result of an insufficient intake of vitamins and minerals, often referred to as ‘hidden hunger’. A deficiency of one or more vitamins may result in a deficiency disease, such as scurvy, beriberi, rickets, osteomalacia and others, depending on which vitamin is insufficient in the body. Where there is inadequate intake of vitamins compared to recommendations, individuals can experience serious, long-term health implications and increased susceptibility to disease. As chronic disease levels rise globally, health and wellbeing remain significant concerns for governments and healthcare systems worldwide. In developed countries, rising healthcare costs and the burden of caring for aging populations provide additional challenges. As such, there is a greater need for the development of effective, nutritional solutions that address individual health concerns and lifestyle needs.

Vitamins play a role in several market segments, including early life nutrition, food and beverage, dietary supplements, public health, and medical nutrition, as well as the pharmaceutical industry, where vitamins are used as active pharmaceutical ingredients (APIs).

Early life nutrition
Emerging science shows that good nutrition during pregnancy and infancy can ‘program’ the immediate and long-term health of a growing baby. It is therefore important that women and babies receive the necessary nutrients at appropriate levels during the first 1,000 days – the period between the onset of a woman’s pregnancy and her child’s second birthday – to provide the foundation for a healthy childhood, adolescence and adulthood.

Food and beverage
People often find it difficult to incorporate nutrient dense food into their diet i.e. food that provides a high proportion of key nutrients relative to its energy content. In these instances, fortified food and beverages can offer a convenient and cost-effective solution to help prevent nutrient shortfalls and associated inadequacies and promote long-term optimal health.

Dietary supplements
To achieve adequate and optimal nutrient status in the body and support good health throughout life, there is a need to address the nutritional balance within the diet. Dietary supplements can complement normal food and offer consumers a convenient and effective solution to ensure optimal intake and status of specific vitamins, preventing nutrient shortfalls and the associated inadequacies or even deficiencies.

Public health
As the world’s population increases and ‘hidden hunger’ (i.e. malnutrition caused by chronic inadequate intake of essential vitamins and minerals, despite sufficient intake of calories) affects more people worldwide, optimized nutrition is becoming ever more critical. As well as fortification of foods, multiple micronutrient supplements, micronutrient powders and lipid-based nutrient supplements have been proven to be effective at helping vulnerable population groups achieve optimum nutrition.

Medical nutrition
Vitamins used in specialized medical nutrition solutions for the management of a health condition or disease are critical to recovery, both for patients and for elderly populations that are not able to meet adequate nutrient requirements via normal food. Specialized medical nutrition products that address disease and age-related malnutrition include solutions for oral nutritional supplements (ONS), enteral nutrition and parenteral nutrition.

Pharmaceutical applications
Therapeutic uses of vitamins cover a wide range of medical conditions. Emerging research suggests that vitamins, alone or in combination with other drugs, may provide a new and low risk treatment strategy for certain diseases. Because they are essential nutrients, vitamins are inherently biocompatible and typically have an established safety profile.
Peter van Dael
Senior Vice President,
Nutrition Science & Advocacy

The global population is growing rapidly year-on-year and people are living longer than ever before. While this is an excellent example of how far we have come in terms of scientific and medical advances, with this aging population comes an increased responsibility for the food, beverage and dietary supplements industries, as well as governments and health authorities, to support health and wellbeing throughout life. Hidden hunger has become a significant problem in both developing and developed countries, affecting approximately two billion people worldwide. Although progress has been made in tackling the problem, hidden hunger still remains an important challenge to overcome.

As a purpose-led, global science-based company in Nutrition, Health and Sustainable Living, DSM will continue to transform as the world does – just as we have throughout history – using our bright science to keep the growing population healthy. We have the ambition to make the world a better place, and we are thinking about tomorrow, today. Our science is already making a big impact, but only together can we create a healthier, more sustainable future. For more than 11 years, we have partnered with the World Food Programme (WFP) to help deliver nutritious food to more than 31 million beneficiaries around the world. Additionally, DSM Scientific Services, a trusted leader in connecting people to science-led knowledge on human nutrition and health, helps to educate people on hidden hunger and chronic malnutrition, as we strive to end hunger in all its forms.

Hidden hunger has become a significant problem in both developing and developed countries.

I am a strong believer that the key to improving consumer health and nutrition, and combating hidden hunger, is scientific research and continuous innovation. While we have already achieved a significant amount in the last 100 years of vitamin research, malnutrition persists and there are still knowledge gaps among the scientific community. As such, current and future research must focus on addressing the biggest issues in nutrition, which include improving and adjusting the recommendations for micronutrient consumption worldwide to today’s lifestyles.

As pioneers in vitamin research and experts in nutritional science, we play a pivotal role in providing science-based information and in educating the population about the importance of sustainable nutrition. Sharing best practices and scientific knowledge, as well as having a clear understanding of different cultural dietary preferences, are all critical to innovate and are actions that we strongly encourage the entire food industry to take. With new insights and continued research, we can then find innovative and increasingly personalized ways to keep the growing and aging population healthy.

Current and future research must focus on addressing the biggest issues in nutrition.
The complete history of vitamins

The discovery of vitamins

While several physicians, researchers and experts had previously linked healthy eating to healthy bodies, vitamins were not actually discovered until 1912, when Polish scientist, Dr. Casimir Funk, isolated thiamine, or vitamin B1, in rice bran. Funk realized that thiamine could cure patients of beriberi, a disease now known to be caused by deficiency of the nutrient. At the time, he named the special nutritional components of food ‘vitamines’, after ‘vita’ meaning vitally important, or life, and ‘amine’, an organic derivative of ammonia, however, they later came to be known as vitamins.

Since the discovery of thiamine, there have been significant advances in vitamin research. In 1916, American biochemist Elmer V McCollum introduced the letters A, B, C and D, that we are so familiar with today, to identify each vitamin. Throughout the 20th century, most notably in the 1920s, there were many scientific breakthroughs in the world of vitamins, as researchers continued to isolate and identify various vitamins found in food. During this decade, vitamin C was discovered as the antiscorbutic factor in food, vitamin D was identified by irradiating food to treat rickets, vitamin E in vegetable oils, and vitamin K in cholesterol-rich diets. By 1941 all 13 vitamins had been determined and characterized (figure 2).

Winning science: 12 Nobel prizes have been awarded over the years for outstanding advances in vitamin science.

### Vitamin Alternative name Discovery Isolation Structure Synthesis

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Alternative name</th>
<th>Discovery</th>
<th>Isolation</th>
<th>Structure</th>
<th>Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Retinol</td>
<td>1910</td>
<td>1931</td>
<td>1931</td>
<td>1947</td>
</tr>
<tr>
<td>β-Carotene</td>
<td>Provitamin A</td>
<td>1931</td>
<td>1931</td>
<td>1931</td>
<td>1950</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Calciferol</td>
<td>1919</td>
<td>1932</td>
<td>1936</td>
<td>1959</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Tocopherol</td>
<td>1922</td>
<td>1936</td>
<td>1938</td>
<td>1938</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Phylloquinone</td>
<td>1929</td>
<td>1939</td>
<td>1939</td>
<td>1939</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Ascorbic acid</td>
<td>1912</td>
<td>1928</td>
<td>1933</td>
<td>1933</td>
</tr>
<tr>
<td>Vitamin B1</td>
<td>Thiamine</td>
<td>1897</td>
<td>1912</td>
<td>1936</td>
<td>1936</td>
</tr>
<tr>
<td>Vitamin B2</td>
<td>Riboflavin</td>
<td>1920</td>
<td>1933</td>
<td>1935</td>
<td>1935</td>
</tr>
<tr>
<td>Vitamin B3</td>
<td>Niacin</td>
<td>1936</td>
<td>1936</td>
<td>1937</td>
<td>1994</td>
</tr>
<tr>
<td>Vitamin B5</td>
<td>Pantothenic acid</td>
<td>1931</td>
<td>1938</td>
<td>1940</td>
<td>1940</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>Pyridoxine</td>
<td>1934</td>
<td>1938</td>
<td>1938</td>
<td>1938</td>
</tr>
<tr>
<td>Vitamin B7</td>
<td>Biotin</td>
<td>1931</td>
<td>1935</td>
<td>1942</td>
<td>1943</td>
</tr>
<tr>
<td>Vitamin B9</td>
<td>Folic acid</td>
<td>1941</td>
<td>1941</td>
<td>1946</td>
<td>1946</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Cobalaminis</td>
<td>1926</td>
<td>1948</td>
<td>1956</td>
<td>1972</td>
</tr>
</tbody>
</table>
Paving the way for major advances in nutrition science

Eventually, this period of discovery would pave the way for major advancements in nutrition science and lead to the development of the nutritionally rich foods and supplements that are so commonplace today (Figure 3). In order for people to benefit from vitamins without relying on dietary intake alone, breakthroughs in vitamin production, formulation and application were required. Pharmaceutical companies, namely in Europe and the US, were inspired to develop synthetic routes and formulation technology applications following the new vitamin research that was emerging. In 1934, pharmaceutical giant, Hoffmann-La Roche, became the first company to produce vitamins on an industrial scale. In the years that followed, all vitamins were to become available via chemical synthesis, fermentation or extraction from natural sources, offering opportunities to fortify diets or use as supplements.

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Main functions</th>
<th>Risks in state of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Visual pigments in the retina; cell differentiation</td>
<td>Night blindness, xerophthalmia; keratinization of skin</td>
</tr>
<tr>
<td>β-Carotene</td>
<td>Antioxidant</td>
<td>No known adverse side effects of a low carotenoid diet, provided vitamin A intake is adequate</td>
</tr>
<tr>
<td>D</td>
<td>Maintenance of calcium balance; enhances intestinal absorption of Ca2+ and mobilizes bone mineral</td>
<td>Rickets (poor mineralization of bone); osteomalacia (de-mineralization of bone)</td>
</tr>
<tr>
<td>E</td>
<td>Antioxidant, especially in cell membranes</td>
<td>Extremely rare: serious neurological dysfunction</td>
</tr>
<tr>
<td>K</td>
<td>Coenzyme in formation of β-carboxyglutamate in enzymes of blood clotting and bone matrix</td>
<td>Impaired blood clotting, hemorrhagic disease</td>
</tr>
<tr>
<td>C</td>
<td>Coenzyme in hydroxylation of proline and lysine in collagen synthesis; antioxidant enhances absorption of iron</td>
<td>Scurvy, impaired wound healing, loss of dental cement, subcutaneous hemorrhage</td>
</tr>
<tr>
<td>B1</td>
<td>Coenzyme in pyruvate and 2-keto-glutarate dehydrogenases and transketolase; poorly defined function in nerve conduction</td>
<td>Peripheral nerve damage (beriberi) or central nervous system lesions (Wernicke-Korsakoff syndrome)</td>
</tr>
<tr>
<td>B2</td>
<td>Coenzyme in oxidation and reduction reactions; prosthetic group of flavoproteins</td>
<td>Lesions of corner of mouth, lips, and tongue: seborrheic dermatitis</td>
</tr>
<tr>
<td>B3</td>
<td>Coenzyme in oxidation and reduction reactions, functional part of NAD and NADP</td>
<td>Pellagra, photosensitive dermatitis, depressive psychosis</td>
</tr>
<tr>
<td>B5</td>
<td>Functional part of coenzyme A and acyl carrier protein</td>
<td>Peripheral nerve damage (burning foot syndrome)</td>
</tr>
<tr>
<td>B6</td>
<td>Coenzyme in transamination and decarboxylation of amino acids and glycoprotein phosphorylase; role in steroid hormone action</td>
<td>Disorders of amino acid metabolism, convulsions</td>
</tr>
<tr>
<td>B7</td>
<td>Coenzyme in carboxylation reactions in gluconeogenesis and fatty acid synthesis</td>
<td>Impaired fat and carbohydrate metabolism, dermatitis</td>
</tr>
<tr>
<td>B9</td>
<td>Coenzyme in transfer of one carbon fragments</td>
<td>Megaloblastic anemia, neural tube defects</td>
</tr>
<tr>
<td>B12</td>
<td>Coenzyme in transfer of one carbon fragments</td>
<td>Pernicious anemia (megaloblastic anemia with degeneration of the spinal cord)</td>
</tr>
</tbody>
</table>

Figure 3: Biochemical function of vitamins
Malnutrition – a global challenge

By the 1940s, leading authorities had already established dietary standards and nutrient recommendations for the required and safe intake of vitamins, depending on age, gender and risk groups. Since then, mandatory fortification programs have been established in the majority of countries across the world to ensure sufficient vitamin intake among populations.

However, despite these efforts and recommendations, inadequate vitamin intake and status still remains a globally prevalent issue and is considered one of the most significant public health challenges of the 21st century. In fact, the majority of the world’s population achieves lower than recommended intake, and status, of one or more essential vitamins. In addition to this, the population is aging rapidly around the globe. With insufficient vitamin intake linked to long-term health implications, this is creating significant burdens on societies and healthcare systems. As such, addressing the nutritional gap to improve the lives of millions of people worldwide has become a significant priority for food, beverage and supplement manufacturers, as well as governments, non-governmental organizations, healthcare professionals and nutrition experts.

The increasing burden of hidden hunger

Nutrient-dense foods are those that are high in nutrients, such as vitamins and minerals, but relatively low in calories. Consumption of nutrient-dense foods associated with lower energy intakes results in a higher quality of diet and improved health outcomes. However, a third of the world’s population suffers from ‘hidden hunger’ i.e. malnutrition caused by chronic inadequate intake of essential vitamins and minerals, despite sufficient intake of calories. Most people affected by hidden hunger do not show the physical symptoms usually associated with hunger and malnutrition. As a result, micronutrient insufficiency has largely been ignored until recently and is considered a new health challenge. With the increasing aging population and prevalence of disease, there is a need to raise awareness of, and re-balance, the nutrient-energy density within food products and solve the hidden hunger issue. Here, clear nutritional labeling is important, as it gives maximum transparency and allows people to make healthier food choices.
Continued vitamin innovation

After more than 100 years since the discovery of vitamins, ongoing scientific research still provides fresh insights into their role in supporting health and wellbeing, as well as getting us closer to determining the appropriate nutritional doses and dietary reference intakes (DRIs). More recently, pharmaceutical doses are also being explored in clinical trials to establish how vitamin APIs can support humans beyond day-to-day health and wellbeing.

Dietary reference intakes (DRIs)

DRIs are the recommended levels for specific nutrients and consist of the following types of recommendations:

- Estimated Average Requirement (EAR)
- Recommended Daily Intake (RDI)
- Tolerable Upper Intake Level (UL)

In the graph above, the RDI is set to meet the nutritional needs of 97-98% of a population and is higher than the EAR. The left curve shows progressive reduction of the risk of inadequacy with increased intake. After that, there is a range where an individual can consume more of a nutrient, before hitting the UL where adverse effects may appear. So, while the RDI sets the target, the UL sets the limit.

DRIs are not minimum or maximum nutritional requirements, nor are they intended to fit everybody, and should be used only as guides for healthy populations and not for those who are ill or malnourished. DRIs can help healthy people determine whether intake of a particular nutrient is adequate and are used by healthcare professionals and policy makers to determine nutritional recommendations for special groups of people, who may need help reaching nutritional goals.

Figure 4. A theoretical framework of the DRI values

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Guide to all 13 vitamins

Health benefit solutions
DSM’s extensive portfolio of Health Benefit Solutions targets specific areas of health and lifestyle to ensure consumers have access to innovative and appealing nutrition products to suit their needs. Every solution utilizes DSM’s strong scientific heritage and diverse portfolio of high-quality ingredients and custom premixes, as well as its broad technical and regulatory network and expertise in market positioning and marketing.

Vitamin A

Synonyms:
Retinol, axerophthol.

Chemistry:
Retinol and its related compounds consist of four isoprenoid units joined head to tail and contain five conjugated double bonds. They naturally occur as alcohol (retinol), as aldehyde (retinal) or as acid (retinoic acid).

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>Retinol (μg)</th>
<th>Serving (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, tuna fish</td>
<td>200,000</td>
<td>150</td>
</tr>
<tr>
<td>Liver, pig</td>
<td>28,000</td>
<td>150</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>24,000</td>
<td>20</td>
</tr>
<tr>
<td>Eel</td>
<td>1,050</td>
<td>100</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>700</td>
<td>19</td>
</tr>
<tr>
<td>Camembert cheese</td>
<td>380</td>
<td>30</td>
</tr>
<tr>
<td>Salmon</td>
<td>40</td>
<td>150</td>
</tr>
<tr>
<td>Chicken</td>
<td>39</td>
<td>150</td>
</tr>
<tr>
<td>Mice’s milk, whole</td>
<td>33</td>
<td>200</td>
</tr>
<tr>
<td>Beef (muscles)</td>
<td>20</td>
<td>150</td>
</tr>
<tr>
<td>Pork (muscles)</td>
<td>6</td>
<td>150</td>
</tr>
<tr>
<td>Veal (muscles)</td>
<td>0.1</td>
<td>150</td>
</tr>
</tbody>
</table>

Main functions:
- Vision
- Differentiation of cells
- Fertility
- Embryogenesis, growth and development
- Immunity
- Intact epithelia

For scientific sources, please contact info.nutritionscience@dsm.com.
Vitamin A

Vitamin A is a generic term for a group of fat-soluble compounds found in animal sources (where it is referred to as ‘preformed vitamin A’ or ‘retinol’) and in fruits and vegetables (where it is known as ‘provitamin A carotenoid’). Vitamin A has multiple functions in the body but it is considered essential for vision, especially night vision, growth and development, and immune health. Due to its unique role in normal vision, one of the earliest symptoms of its deficiency is night blindness.

Functions

Retinal, the oxidized metabolite of retinol, is essential for normal vision. Retinoic acid, on the other hand, is considered to be responsible for almost all non-visual functions relating to vitamin A. Retinoic acid acts by binding to the retinoic acid receptor (RAR), which is attached to DNA responsible for the expression of more than 500 genes. This influences numerous physiological processes and induces hormone-like activity.

Vision

Receptor cells, also known as rod cells, in the retina of the eye contain a light-sensitive pigment called rhodopsin – a complex of the protein opsin and vitamin A metabolite retinal. The light-induced disintegration of the pigment triggers a cascade of events generating an electrical signal to the optic nerve and promoting vision. Rod cells with this pigment can even detect very small levels of light, making them important for night vision.

Cellular differentiation

The many different types of cells in the body perform highly specialized functions. The process whereby cells and tissues become ‘programmed’ to carry out their special functions is called differentiation. Through the regulation of gene expression, retinoic acid plays a major role in cellular differentiation. In fact, vitamin A is necessary for the normal differentiation of epithelial cells i.e. the cells of all tissues lining the body, including skin, mucous membranes, blood vessel walls and the cornea. If cells are deficient in vitamin A, they lose their ability to differentiate properly.

Growth and development

Retinoic acid plays an important role in reproduction and embryonic development, particularly in the development of the spinal cord and vertebrae, limbs, heart, eyes and ears.

Immune function

Vitamin A is also required for normal immune function. It is essential in maintaining the integrity and performance of skin and mucosal cells, which act as a mechanical barrier to pathogens and defend the body against infection. Vitamin A also plays a central role in the development and differentiation of white blood cells, such as lymphocytes, killer cells and phagocytes, which play a critical role in the defense of the body against disease.

Dietary sources

The richest food source of preformed vitamin A is liver, with considerable amounts also found in egg yolks, dairy products and fish. Provitamin A carotenoids are predominantly found in carrots, yellow and dark green leafy vegetables (e.g. spinach, broccoli), pumpkin, apricots and melon. Until recently, vitamin A activity in foods was expressed as international units (IU). This unit is still the measurement generally used on food and supplement labels; however, nutrition scientists now use retinol activity equivalent (RAE), which accounts for the rate of conversion of carotenoids to retinol.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&gt;6 months</td>
<td>400 µg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>500 µg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>300 µg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>400 µg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>600 µg</td>
</tr>
<tr>
<td>Males</td>
<td>&gt;14 years</td>
<td>900 µg</td>
</tr>
<tr>
<td>Females</td>
<td>&gt;14 years</td>
<td>700 µg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 18 years</td>
<td>750 µg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>&gt;19 years</td>
<td>770 µg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 18 years</td>
<td>520 µg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>&gt;19 years</td>
<td>5,300 µg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2001)  
** As RAEs adequate intake (AI)

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.
Deficiency
Vitamin A deficiency increases the risk of morbidity and mortality, especially in infants, children, pregnant women and breastfeeding mothers. Worldwide, it is estimated that 250 million pre-school children are vitamin A deficient resulting in 250,000 – 500,000 children becoming blind each year. This makes vitamin A deficiency one of the most widespread, yet preventable, causes of blindness in developing countries. The earliest symptom of vitamin A deficiency is impaired dark adaptation, also known as night blindness. Severe deficiency can cause xerophthalmia, a condition characterized by changes in the cells of the cornea that result in corneal ulcers, scarring and blindness. The appearance of skin lesions is also an early indicator of inadequate vitamin A status. Because vitamin A is required for the normal functioning of the immune system, even children who are only mildly deficient in the micronutrient have a higher incidence of respiratory disease and diarrhea, as well as an increased risk of mortality from infection. Some diseases may induce vitamin A deficiency, most notably liver and gastrointestinal diseases, which interfere with the absorption and utilization of vitamin A.

Groups at risk
• Pregnant and breastfeeding women
• Infants, young children and adolescents
• Alcoholics
• Individuals with a chronic illness
• Individuals with protein malnutrition and malabsorption
• Vegetarians and vegans with additional polymorphisms in the BCM01 gene

Reducing disease risk: therapeutic use
Studies have shown that vitamin A supplementation given to children aged 6 months or older reduces all-cause mortality by 23% to 30% in low income countries. The WHO recommends that supplements are given when children are vaccinated. The currently daily recommended doses of vitamin A are 1,366 IU at age 6 – 11 months and 1,333 IU at age >12 months. Xerophthalmia (vitamin A deficiency) is treated with high doses of the vitamin (50,000 – 200,000 IU daily according to age). In developing countries, where vitamin A deficiency is one of the most serious health problems, children under the age of 6 years and pregnant and breastfeeding women are the most vulnerable groups. Since vitamin A can be stored in the liver, it is possible to build up a reserve in children by administration of high-potency doses. In regular periodic distribution programs for the prevention of vitamin A deficiency, infants <6 months of age receive a dose of 50,000 IU of vitamin A, children between six months and one year receive 100,000 IU every 4 – 6 months and children >12 months of age receive 200,000 IU every 4 – 6 months. A single dose of 200,000 IU given to mothers immediately after delivery of their child has also been found to increase the vitamin A content of breast milk. However, caution is necessary when considering vitamin A therapy for breastfeeding women as it may pose a risk to a co-existing pregnancy. During pregnancy, a daily dose of 4,333 IU should not be exceeded.

Recommended Daily Intake (RDI)
The recommended daily intake of vitamin A varies according to age, sex, risk group and other criteria applied in individual countries.

Safety
Because vitamin A (as retinyl ester) is stored in the liver, large amounts taken over a period of time can eventually exceed the liver’s storage capacity and produce adverse effects, such as liver damage, bone abnormalities and joint pain, aloppecia, headaches, vomiting and skin peeling. On the other hand, hypervitaminosis A can occur acutely following very high doses of the micronutrient taken over a period of several days or as a chronic condition from high doses taken over a long period of time. Thus, there is concern about the safety of high intakes of preformed vitamin A (retinol), especially for infants, small children and women of childbearing age. For example, normal fetal development requires sufficient vitamin A intake, but consumption of excess retinol during pregnancy is known to cause malformations in the newborn. In addition, several studies suggest that long-term intakes of pre-formed vitamin A in excess of 1,500 μg/day are associated with increased risk of osteoporotic fracture and decreased bone mineral density in older men and women. Only excess intakes of preformed vitamin A, not β-Carotene, were associated with adverse effects on bone health. Current levels of vitamin A in fortified foods are based on RDI levels, ensuring that there is no realistic possibility of vitamin A overdose in the general population. In the majority of cases, signs and symptoms of toxicity are reversible upon cessation of vitamin A intake.

The Food and Nutrition Board of the Institute of Medicine (IOM, 2001) and the E.C. Scientific Committee on Food (2002) have set the tolerable upper intake level (UL) of vitamin A as 1,000 μg/day of vitamin A intake for adults at 3000 μg RE/day with appropriately lower levels for children.

Supplements and food fortification
Vitamin A is available in soft gelatin capsules, as chewable or fizzy tablets, or in ampoules (a small sealed glass capsule). It is also included in most multivitamins and supplements as retinyl acetate, retinyl palmitate and retinol. Margarine and milk are also commonly fortified with vitamin A. β-Carotene may also be added to margarine and many other foods, such as fruit drinks, salad dressings, cakes, mix ice cream both for its vitamin A activity and as a natural food colorant.

Production
Nowadays vitamin A is rarely extracted from fish liver oil. The modern method of industrial synthesis of nature-identical vitamin A is a highly complex, multi-step process.
β-Carotene

Chemistry:
β-Carotene is a red-orange pigment and a member of the carotenes, which are terpenoids. It is made up of eight isoprene units, which are cyclized at each end. The long chain of conjugated double bonds is responsible for the orange color of β-Carotene.

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
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<tbody>
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</tr>
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<td>Cantaloupes</td>
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<tr>
<td>Broccoli</td>
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</tr>
<tr>
<td>Pumpkins</td>
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</tr>
<tr>
<td>Asparagus</td>
<td>0.5</td>
</tr>
<tr>
<td>Peaches</td>
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</tr>
</tbody>
</table>

(Main functions:
• Source of vitamin A (provitamin A)
• Antioxidant
• Sun protection (UV-filter)

β-carotene is a member of the carotenoid family, which is made up of the red, orange and yellow fat-soluble pigments naturally present in many fruits, grains, oils and vegetables. Of the naturally occurring carotenoids that can be converted to vitamin A in the body, β-carotene is the most abundant and efficient form found in foods. However, as well as being a safe source of vitamin A, β-carotene also functions as an antioxidant and a sun protection agent.

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
β-Carotene is the most important dietary source of vitamin A and is critical for normal human function. Vitamin A is essential for normal growth and development, immune response and vision. β-Carotene’s antioxidant properties are well documented, helping to neutralize free radicals – reactive and highly energized molecules, which are formed through normal biochemical reactions (e.g. the immune response and prostaglandin synthesis), or through exogenous sources such as air pollution or cigarette smoke. Free radicals can damage lipids in cell membranes, as well as DNA in cells. The resulting damage may lead to the development of cancer in some individuals. β-Carotene is also known to provide protection against skin damage from sunlight.

Dietary sources
The best sources of β-Carotene are yellow or orange vegetables, as well as fruits and dark green leafy vegetables:
- **Yellow/orange vegetables:**
  - Carrots, sweet potatoes, pumpkins, winter squash
- **Yellow/orange fruits:**
  - Apricots, cantaloupes, papayas, mangoes, carambolas, nectarines, peaches
- **Dark green leafy vegetables:**
  - Spinach, broccoli, endive, kale, chicory, escarole, watercress
- **Additional sources:**
  - Summer squash, asparagus, peas, sour cherries, prune plums

Bioavailability of β-Carotene
Bioavailability refers to the proportion of β-Carotene that can be absorbed, transported and utilized by the body once it has been consumed. It is influenced by a number of factors:
- **β-Carotene from dietary supplements is better absorbed than β-Carotene from foods.**
- **Food processing such as chopping, mechanical homogenization and cooking enhances the bioavailability of β-Carotene.**
- **The presence of fat in the intestine affects absorption of β-Carotene.** The amount of dietary fat required to ensure carotenoid absorption is low (approximately 3 – 5 g per meal).

Measurement
Plasma carotenoid concentration, which reflects the intake of carotenoids, is determined by HPLC (high performance liquid chromatography). Traditionally, vitamin A activity of β-Carotene has been expressed in International Units (IU; 1 IU = 0.60 µg of β-Carotene). However, this conversion factor does not consider the poor bioavailability of carotenoids in humans. Thus, the Food and Agriculture Organization (FAO) and Expert Committee propose that vitamin A activity be expressed as retinol activity equivalent (RAE). 12 µg β-Carotene provides 1 µg retinol. For labeling, official national directives should be followed.

Absorption and body stores
Bile salts and fats are needed for the absorption of β-Carotene in the upper small intestine. Many dietary factors, e.g. fat and protein, therefore affect absorption. For instance, approximately 10% to 50% of the total β-Carotene consumed is absorbed in the gastrointestinal tract. The proportion of carotenoids absorbed decreases as dietary intake increases. Within the intestinal wall, also known as the mucosa, β-Carotene is partially converted into vitamin A (retinol) by the enzyme β-Carotene monoxygenase 1 (BCMO1), with this mechanism being regulated by the individual’s vitamin A status. So, if the body has enough vitamin A, the conversion of β-Carotene decreases. Therefore, β-Carotene is a very safe source of vitamin A and high intakes will not lead to excess vitamin A in the body. Any additional β-Carotene is stored in the fat tissues of the body and the liver. This is why an adult’s fat stores are often yellow from accumulated carotene while an infant’s fat stores are white.

Stability
Carotenoids can lose some of their activity in foods during storage due to the action of enzymes and exposure to light and oxygen. Dehydration of vegetables and fruits may also greatly reduce the biological activity of carotenoids. On the other hand, carotenoid stability is retained in frozen foods.

Physiological interactions
- **Vitamins C and E stabilize and rescue β-Carotene**
- **Chronic liver and kidney diseases may impair storage and transport of β-Carotene**
- **Alcohol abuse hampers the capacity of β-Carotene storage**
- **Protein malnutrition, as well as general malabsorption, can influence and decrease the transport and uptake of β-Carotene within the intestine**
- **Reduced blood levels of lutein**

Deficiency
Although consumption of provitamin A carotenoids can prevent vitamin A deficiency, there are no known adverse clinical effects of a low carotenoid diet, provided vitamin A intake is adequate.

Groups at risk
- Pregnant and breastfeeding women
- Infants, young children and adolescents
- Alcoholics (alcohol hampers the capacity of vitamin A storage)
- Individuals with a chronic illness, i.e. cystic fibrosis patients
- Individuals with protein malnutrition and malabsorption
- Vegetarians and vegans with additional polymorphisms in the BCMO1 gene

Reducing disease risk: therapeutic use
**Immune system**
In a number of animal and human studies, β-Carotene supplementation was found to enhance certain immune responses. For example, β-Carotene and other carotenoids, have been proven to prevent infections. Research shows it can lead to an increase in the number of white blood cells and the activity of natural killer cells, which are important in combating multiple diseases. It may be the case that β-Carotene stimulates the immune system once it has undergone conversion to vitamin A. The antioxidant actions of β-Carotene protect cells of the immune system from damage by reducing the toxic effects of reactive oxygen species.

**Skin**
Evidence has shown that β-Carotene may have a role in protecting the skin from sunlight damage. β-Carotene can be used as an oral sun protectant in combination with sunscreens for the prevention of sunburn. Its effectiveness has been shown both alone and in combination with other carotenoids or antioxidant vitamins.

**Erythropoietic protoporphyria**
In patients with erythropoietic protoporphyria – a photosensitivity disorder leading to abnormal skin reactions to sunlight – β-Carotene in doses of up to 180 mg has been shown to have a photoprotective effect.
Recommended Daily Intake (RDI)

Until recently, dietary intake of β-Carotene has been expressed as part of the RDI for vitamin A. The daily vitamin A requirements for adult men and women are 900 µg and 700 µg of preformed vitamin A (retinol) respectively. However, data continues to support a role for β-Carotene as an important micronutrient in its own right. Consumption of foods rich in β-Carotene is therefore being recommended by scientific and government organizations. In Europe and the US, recommended intakes range from 2 mg to 6 mg β-Carotene per day for adults.

Safety

β-Carotene is a safe source of vitamin A. Due to the regulated conversion of β-Carotene into vitamin A, overconsumption does not produce hypervitaminosis A. Excessive intakes of β-Carotene may cause carotenodermia, which manifests itself in a yellowish tint of the skin, mainly in the palms of the hands and soles of the feet. The yellow color disappears when carotenoid consumption is reduced or stopped.

High doses of β-Carotene (up to 180 mg/day), used for the treatment of erythropoietic protoporphyria, have shown no adverse effects.

The British Expert Committee on Vitamins and Minerals (EVM) recommends a UI for supplementation of 7 mg/day over a life-time period. The level of supplemental intake of β-Carotene for which epidemiological studies did not reveal any increased cancer risk or adverse health effects in the general population is 15 mg/day (Latest evaluation by the European Food Safety Authority (EFSA) in March 2012).

Supplements and food fortification

β-Carotene is available in hard and soft gelatin capsules, in multi-vitamin tablets, antioxidant vitamin formulas and as food color. Margarine and fruit drinks are also often fortified with β-Carotene. In 1941, the FDA (US Food and Drug Administration) established a standard of identity for the addition of vitamin A to margarine. Since then, however, vitamin A has been partly replaced by β-Carotene, which additionally imparts an attractive yellowish color to this product. Due to its high safety margin, β-Carotene has been recognized as more suitable for fortification purposes than vitamin A.

Production

Isler and team developed a method to synthesize β-Carotene and it has been commercially available in crystalline form since 1954.

History

- 1831: Wackenroder isolates the orange-yellow pigment in carrots and coins the term ‘carotene’.
- 1887: Willstatter and Mieg establish the molecular formula for carotene, a molecule consisting of 40 carbon and 56 hydrogen atoms.
- 1907: Steenbock suggests a relationship between yellow plant pigments (β-Carotene) and vitamin A.
- 1914: Palmer and Eckles discover the presence of carotene and xanthophylls in human blood plasma.
- 1919: Moore demonstrates that β-Carotene is converted into the colorless form of vitamin A in the liver.
- 1929: Karrer and collaborators determine the structures of β-Carotene and vitamin A.
- 1931: Isler and colleagues develop a method for synthesizing β-Carotene.
- 1950: β-Carotene is found acceptable for use in foods by the Joint FAO/WHO Expert Committee on Food Additives.
- 1966: Isler and colleagues develop a method for synthesizing β-Carotene.
- 1972: Specifications for β-Carotene use in foods is established by the US Food Chemicals Codex.
- 1979: β-Carotene (carotenoids) are recognized as important factors in potentially reducing the risk of certain cancers.
- 1981: Carotene is established as ‘GRAS’, which means that the ingredient is ‘Generally Recognized As Safe’ and can be used as a dietary supplement or in food fortification.
- 1984: Due to the large number of epidemiological studies that demonstrate the potential reduction of cancer incidence with increased consumption of dietary β-Carotene, the US National Cancer Institute (NCI) issues dietary guidelines advising Americans to include a variety of vegetables and fruits in their daily diet.
- 2004: Results from the French SU.VI.MAX study indicate that a combination of antioxidant vitamins (C, E and β-Carotene) and minerals lowers total cancer incidence and all-cause mortality in men.
Vitamin D comprises a group of fat-soluble compounds that are essential for regulating the amount of calcium and phosphate in the body i.e. the nutrients needed to keep bones, teeth and muscles healthy. It is synthesized by the skin when exposed to UV light, such as sunlight. However, it can also be found in some foods including oily fish, red meat, liver and egg yolks, as well as fortified foods and dietary supplements. If vitamin D deficiency occurs, individuals may experience rickets, a frequent childhood disease in many developing countries, or osteoporosis, also known as ‘brittle bone’ disease.
It has also been suggested that vitamin D plays an important role for the proper functioning of muscles, nerves and blood clotting and for normal bone formation and mineralization.

To perform its biological functions, 1,25(OH)2D, like other hormones, binds to a specific nuclear receptor (vitamin D receptor, VDR).

Vitamin D is found only in a few foods. The richest natural sources of vitamin D are fish liver oils and salt-water fish such as sardines, herring, salmon and mackerel. Eggs, meat, milk and butter also contain small amounts, and plants are considered poor sources, with fruit and nuts containing no vitamin D at all. The amount of vitamin D in breastmilk is often insufficient to cover infant requirements, and needs to be supplemented.

Absorption and body stores

Absorption of dietary vitamin D takes place in the upper part of the small intestine with the aid of bile salts. It is stored in adipose tissue and must be metabolized to become active and carry out its biological functions.

Vitamin D status is best determined by the plasma 25(OH)D concentration as this reflects dietary sources, as well as vitamin D production by UV light in the skin. Usual plasma 25(OH)D values are between 25 and 130 nmol/L depending on geographic location. 1 μg vitamin D is equivalent to 40 IU (international unit). Concentrations less than 25 nmol/L are considered to be deficient.

Stability

Vitamin D is relatively stable in foods. Storage, processing and cooking have little effect on its activity, although in fortified milk up to 40% of the vitamin D added may be lost as a result of exposure to light.

Deficiency

Vitamin D deficiency leads to increased parathyroid hormone (PTH) levels, followed by a disturbance of the normal calcium and phosphate homeostasis. In children, unspecific symptoms such as restlessness, irritability, excessive sweating and impaired appetite may appear. Prolonged vitamin D deficiency can induce rickets, a condition that is characterized by developmental delay and skeletal abnormalities as a result of decreased calcium and phosphate availability. Rickets also results in inadequate mineralization of tooth enamel leading to tooth decay.

Among the first signs of osteomalacia, a similar condition to rickets in adults, is bone and muscle pain that can progress to muscle weakness and muscular spasms, as well as an increased risk of infection. Severe vitamin D deficiency will result in bone brittleness. Insufficient vitamin D status has also been strongly associated with osteoporosis, a condition where a loss of bone density results in weaker bones and an increased risk of falling, fractures and muscle weakness. Besides the skeletal effects, vitamin D deficiency has also been linked to a heightened risk of chronic diseases, including autoimmune diseases, heart diseases, infectious diseases and type 2 diabetes.

Groups at risk

- All ages living in a geographic location higher than 40 degrees latitude during wintertime
- Individuals with naturally darker skin
- Vegetarians and vegans
- Individuals with little or no sun exposure including:
  - Elderly individuals living in care homes
  - Individuals that avoid sun exposure for cosmetic or health reasons
  - Shift workers and coal miners
  - Individuals with protective dress code (e.g. religious or cultural)
  - Individuals with diseases or illnesses (e.g. skin cancer patients and long term hospitalized patients)
- Certain medical conditions, such as obesity or being underweight, end stage liver disease, renal disease and nutrient malabsorption syndromes (such as cystic fibrosis, coeliac disease and inflammatory bowel disease), or medications, affect vitamin D metabolism
- Infants (if breastmilk contains little vitamin D)

Reducing disease risk: therapeutic use

In the treatment of rickets, a daily dose of 40 µg (1,600 IU) vitamin D usually results in normal plasma concentrations of calcium and phosphorus within 10 days. The dose can be reduced gradually to 10 µg (400 IU) per day after one month of therapy. Vitamin D analogues (synthetic vitamin D) are commonly used in the treatment of inflammatory skin conditions such as psoriasis. Vitamin D is also discussed as a prevention factor for a number of diseases. Results from epidemiological studies and evidence from animal models suggest that the risk of several autoimmune diseases (including multiple sclerosis, insulin-dependent diabetes mellitus and rheumatoid arthritis) may be reduced through adequate vitamin D status.

It is already well-documented that vitamin D plays a major role in the prevention of osteoporosis as vitamin D insufficiency is an important contributing factor in this disease. A prospective study among 72,000 postmenopausal women over a period of 18 years, indicated that women consuming at least 15 μg/d (600IU vitamin D) per day from food and supplements had a 37% lower risk of hip fracture. Evidence from clinical trials suggest that vitamin D supplementation slows down bone mineral density loss and decreases the risk of osteoporotic fracture in men and women. Various surveys and studies indicate that poor vitamin D intake or status may be associated with an increased risk of colon, breast and prostate cancer. Recent studies have also shown that vitamin D3 is up to 87% more potent than vitamin D2, which may explain why vitamin D3 exerts stronger effects on the prevention of fractures and falls.
Supplements and food fortification

Mono-preparations of vitamin D and related compounds are available as tablets, capsules, oily solutions and injections. Vitamin D is also incorporated in combination with vitamin A, calcium and in multivitamins. In many countries, milk and milk products, margarine and vegetable oils fortified with vitamin D serve as a major dietary source of the vitamin.

Recommended Daily Intake (RDI)

In 1997, the Food and Nutrition Board based AI on the assumption that vitamin D is now recommended at 5 μg (200 IU)/day for children through to adulthood. For the elderly, higher intakes of 15 μg to 20 μg (600 - 800IU)/day are also recommended to maintain normal calcium metabolism and maximize bone health, which is essential for the control of normal calcium and phosphate blood concentrations. It is required for the absorption of calcium and phosphate in the small intestine and can maintain blood calcium and phosphate concentrations through bone mobilization and increased reabsorption in the kidney. It has also been suggested that vitamin D plays an important role in controlling cell proliferation, differentiation, immune responses and insulin secretion.

Safety

Vitamin D toxicity has only been associated with excessive supplement intake of daily doses greater than 50,000 IU of vitamin D. Hypervitaminosis D is a potentially serious problem though as it can cause permanent kidney damage, growth retardation, calcification of soft tissues and even death. Mild symptoms of intoxication include nausea, weakness, constipation and irritability. Hypervitaminosis D is not associated with overexposure to the sun because a regulating mechanism prevents overproduction of vitamin D. The upper intake level for vitamin D is set to 1,500 IU/day for infants, 2,500 - 3,000 IU/day for children and 4,000 IU/day for adults.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0 - 12 months</td>
<td>400 IU (10 μg) (AI)</td>
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<tr>
<td>Children</td>
<td>1-18 years</td>
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<tr>
<td>Males</td>
<td>19 - 50 years</td>
<td>600 IU (15 μg)</td>
</tr>
<tr>
<td>Females</td>
<td>19 - 50 years</td>
<td>600 IU (15 μg)</td>
</tr>
<tr>
<td>Males</td>
<td>51 - 70 years</td>
<td>600 IU (15 μg)</td>
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<tr>
<td>Females</td>
<td>51 - 70 years</td>
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<tr>
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<td>800 IU (20 μg)</td>
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<tr>
<td>Females</td>
<td>&gt;70 years</td>
<td>800 IU (20 μg)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 - 50 weeks</td>
<td>600 IU (15 μg)</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 - 50 weeks</td>
<td>600 IU (15 μg)</td>
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* European Food Safety Authority (2010) ** In the absence of adequate exposure to sunlight adequate intake (AI)

The table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

Recommended intakes (RDI) *

<table>
<thead>
<tr>
<th>Age and Sex</th>
<th>RDI - IU/day</th>
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</thead>
<tbody>
<tr>
<td>Infants</td>
<td>400 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>600 (AI)</td>
</tr>
<tr>
<td>19 – 50 yrs</td>
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<td>51 – 70 yrs</td>
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<td>&gt;70 yrs</td>
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<tr>
<td>Pregnancy</td>
<td>600</td>
</tr>
<tr>
<td>Breastfeeding</td>
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** In the absence of adequate exposure to sunlight adequate intake (AI)

Recommended intakes (RDI) *

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<tbody>
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<td>Infants</td>
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<tr>
<td>Children</td>
<td>600 (AI)</td>
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<tr>
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<td>&gt;70 yrs</td>
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<td>Pregnancy</td>
<td>600</td>
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<tr>
<td>Breastfeeding</td>
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Recommended intakes (RDI) *

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<td>Children</td>
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<tr>
<td>Breastfeeding</td>
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** In the absence of adequate exposure to sunlight adequate intake (AI)

Recommended intakes (RDI) *

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<thead>
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<th>Age and Sex</th>
<th>RDI - IU/day</th>
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<td>Breastfeeding</td>
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** In the absence of adequate exposure to sunlight adequate intake (AI)

Recommended intakes (RDI) *

<table>
<thead>
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<th>Age and Sex</th>
<th>RDI - IU/day</th>
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<td>19 – 50 yrs</td>
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<td>&gt;70 yrs</td>
<td>800</td>
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<tr>
<td>Pregnancy</td>
<td>600</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>600</td>
</tr>
</tbody>
</table>

** In the absence of adequate exposure to sunlight adequate intake (AI)}
Vitamin E

Synonyms:
α-, β-, γ-, δ-tocopherol and α-, β-, γ-, δ-tocotrienol.

Chemistry:
A group of compounds composed of a substituted chromanol ring with a C16 side chain saturated in tocopherols, with 3 double bonds in tocotrienols.

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>(μg)/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat germ oil</td>
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<tr>
<td>Sunflower oil</td>
<td>63</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>26</td>
</tr>
<tr>
<td>Rape seed oil</td>
<td>23</td>
</tr>
<tr>
<td>Soya bean oil</td>
<td>17</td>
</tr>
<tr>
<td>Olive oil</td>
<td>12</td>
</tr>
<tr>
<td>Peanuts</td>
<td>11</td>
</tr>
<tr>
<td>Walnuts</td>
<td>6</td>
</tr>
<tr>
<td>Butter</td>
<td>2</td>
</tr>
<tr>
<td>Spinach</td>
<td>1.4</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>0.8</td>
</tr>
<tr>
<td>Apples</td>
<td>0.5</td>
</tr>
<tr>
<td>Milk (whole)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Main functions:
- Major fat-soluble antioxidant
- Non-antioxidant functions in cell signaling, gene expression and regulation of other cell functions

Vitamin E

Vitamin E is found in a wide variety of foods and helps to maintain healthy skin and eyes, acts as an antioxidant and supports the body’s immune defense against illness and infection. No clinical deficiency symptoms of vitamin E have ever been noted in healthy adults. The micronutrient is stored in various tissues, meaning depletion of its stores takes a very long time, although deficiency may occur in individuals with genetic disorders or in premature infants.

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
Vitamin E functions as a lipid soluble antioxidant, preventing the propagation of free-radical reactions. Free radicals are formed in normal metabolic processes upon exposure to exogenous toxic agents, such as cigarette smoke and pollutants. Vitamin E is located within the cellular membranes and protects polyunsaturated fatty acids (PUFAs) and other components of cellular membranes from oxidation by free radicals. Apart from maintaining the integrity of the cell membranes in the human body, it also protects low density lipoproteins (LDL) from oxidation. Additionally, non-antioxidant functions of α-tocopherol have recently been identified, including its ability to inhibit protein kinase C activity, which is involved in cell proliferation and differentiation. Vitamin E is also known to inhibit platelet aggregation and enhances vasodilation (the widening of blood vessels). Furthermore, vitamin E enrichment of endothelial cells down regulates the expression of cell adhesion molecules, thereby decreasing the adhesion of blood cell components to the endothelium.

Dietary sources
Vegetable oils, including olive, soybean, palm, corn, safflower and sunflower oil, as well as nuts, whole grains and wheat germ are the main sources of vitamin E. Seeds, green leafy vegetables, fruits, dairy products, fish and meat also contain vitamin E. At present, the vitamin E content of foods and dietary supplements is listed on labels in international units (IU). Naturally sourced vitamin E is called RRR-α-tocopherol (commonly labeled as d-alpha-tocopherol); the synthetically produced form is all rac-alpha-tocopherol (commonly labeled as dl-alpha-tocopherol). To convert from mg to IU, 1 mg of alpha-tocopherol is equivalent to 1.49 IU of the natural form or 2.22 IU of the synthetic form. When converting from IU to mg, 1 IU of the natural form is equivalent to 0.67 mg alpha-tocopherol and 1 IU of the synthetic form is equal to 0.45 mg of alpha-tocopherol.

Absorption and body stores
Vitamin E is absorbed together with lipids in the small intestine, depending on adequate pancreatic function and biliary secretion. It is then incorporated into chylomicrons and transported via the lymphatic system to the liver. α-tocopherol is the vitamin E form that predominates in blood and tissue, due to the liver protein α-tocopherol transfer protein, which preferentially incorporates α-tocopherol into the lipoproteins. It is then delivered to different tissues throughout the body. The highest vitamin E contents are found in the adipose tissue, liver and muscles. The pool of vitamin E in the plasma, liver, kidneys and spleen turns over rapidly, whereas turnover of the content of adipose tissue is slow.

Measurement
Normal α-tocopherol concentrations in plasma measured by high performance liquid chromatography range from 12 – 45 µM (0.5 – 2 mg/100 ml). Plasma α-tocopherol concentrations of <11.6 µM, the level at which erythrocyte hemolysis occurs, indicates a poor vitamin E nutritional status. Since plasma levels of α-tocopherol correlate with cholesterol levels, the α-tocopherol concentration is often indicated as α-tocopherol-cholesterol ratio. Generally, vitamin E content is expressed by biological activity, using the scale of IU. According to this system, 1 mg of RR-α-tocopherol, biologically the most active of the naturally occurring forms of vitamin E, is equivalent to 1.49 IU vitamin E. The biological activity of 1 mg of all rac-α-tocopheryl acetate, the synthesized form of vitamin E commonly used in food enrichment, is equivalent to 1 IU. Recently, the unit of α-tocopherol equivalent was established (see: Dietary sources).

Stability
Light, oxygen and heat are detrimental factors encountered during long storage periods of foodstuffs and food processing as they reduce the vitamin E content of food. In some cases, vitamin E content can decrease by as much as 50 percent after only two weeks of storage at room temperature. Chemical compounds of α-tocopherol (α-tocopheryl acetate and α-tocopheryl succinate) are often used for supplements because they are more resistant to oxidation during storage.

Physiological interactions
- The presence of other antioxidants, such as vitamin C and β-Carotene, supports the antioxidative and protective action of vitamin E. The same is true for the mineral selenium
- The requirement for vitamin E varies as it is related to the amount of PUFAs consumed by an individual; the higher the amount of PUFAs, the more vitamin E is required
- When taken at the same time, iron reduces the availability of vitamin E to the body, which is especially critical in the case of anemic newborns
- Vitamin K deficiency may be exacerbated by vitamin E, which can affect blood coagulation
- Various medications decrease absorption of vitamin E, including cholestyramine, colestipol and ioniizad retinopathy. Early diagnostic signs are leakage of muscle enzymes, increased plasma levels of lipid peroxidation products and increased hemolysis of erythrocytes (red blood cells). In premature infants, vitamin E deficiency is associated with hemolytic anemia, intraventricular hemorrhage (a condition in which blood vessels within the brain burst and bleed into the ventricles) and retrolental abnormal blood vessel development in the retina of the eye.

Groups at risk
- Vitamin E deficiency may occur as a result of genetic abnormalities in a-TTP, various fat malabsorption syndromes and protein-energy malnutrition

Reducing disease risk: therapeutic use
Research studies indicate that vitamin E has numerous health benefits. It is thought to play a role in preventing atherosclerosis and cardiovascular disease (CVD), i.e. heart disease and stroke, due to its effects on the development of atherosclerosis, such as the inhibition of LDL oxidation, smooth muscle cell proliferation, platelet adhesion, aggregation and platelet release reaction. Studies also suggest that vitamin E enhances immunity in the elderly and that supplementation with vitamin E lowers the risk of contracting an upper respiratory tract infection, particularly the common cold. Researchers are investigating the prophylactic role of vitamin E in protecting against exogenous pollutants and lowering the risk of cancer cataracts. In combination with vitamin C, it may also protect the body from oxidative stress caused by extreme sports, such as ultra-marathon running. Vitamin E supplementation is also under investigation for the treatment of neurodegenerative diseases such as Alzheimer’s disease and amyotrophic lateral sclerosis.
Recommended Daily Intake (RDI)

The recommended daily intake of vitamin E varies and depends on age, sex and country of residence. In the US, the RDI for adults is 15 mg RRR-α-tocopherol/day (FNB, 2000). In Europe, adult recommendations range from 4 to 15 mg α-TE/day for men and from 3 to 12 mg α-TE/day for women. The RDI for vitamin E of 15 mg cannot easily be acquired even with the best nutritional intentions.

Vitamin E intake should also be adapted to the PUFA and the E:C. Scientific Committee on Foods (SCF) has suggested a consumption ratio of 0.4 – 0.6 mg α-TE per gram of PUFA.

Safety

Vitamin E has a low toxicity and after reviewing more than 300 scientific studies, the US-based Institute of Medicine (IOM) concluded that vitamin E is safe for chronic use even at doses of up to 1,000 mg per day. A recently published meta-analysis suggested that taking a high dose of more than 2,000 IU vitamin E per day leads to an increase in the risk of all-cause mortality. However, much of the research was completed in patients at high risk of a chronic disease, therefore these findings may not be applicable to healthy adults.

Moreover, many long-term studies with much higher doses of vitamin E did not report any adverse effects. In fact, meta-analyses with neutral or beneficial outcomes on all-cause mortality have outnumbered the negative ones, and there is no consistent information on how vitamin E might increase risk of mortality. It is therefore generally accepted that vitamin E intakes of up to 1,600 IU (1073 mg RRR-α-tocopherol) are safe for most adults. While in the European Union an upper intake level of 300 mg alpha-tocopherol equivalents per day has been established for adults; in the UK this level has been set at 540 mg/day for supplemental vitamin E, and in the US at 1,000 mg per day for any form of supplemental alpha-tocopherol.

It is important to note that pharmacologic doses of vitamin E may increase the risk of bleeding in patients treated with anticoagulants. Patients on anticoagulant therapy or those anticipating surgery should avoid high levels of vitamin E.

Supplements and food fortification

Vitamin E is available in soft gelatin capsules and as chewable or effervescent tablets. It is also found in most multivitamin supplements. The most common use is in fortified foods, such as soft drinks and cereals.

The all-rac-α-tocopherol form of vitamin E is widely used as an antioxidant in stabilizing edible oils, fats and fat-containing food products. For example, research has shown that vitamin E in combination with vitamin C may reduce the formation of nitrosamines (a proven carcinogen in animals) in pork more effectively than vitamin C alone. Vitamin E has typically been used as an anti-inflammatory agent to enhance skin moisturization and to prevent cell damage by UV light. In pharmaceutical products, tocopherol is used to stabilize syrups, aromatic components, and vitamin A or provitamin A components.

Production

Vitamin E, derived from natural sources, is obtained by molecular distillation and in most cases subsequent methylation and esterification of edible vegetable oil products. Synthetic vitamin E is produced from fossil plant material by condensation of trimethylhydroquinone with isophytol.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>4 mg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>9 mg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>6 mg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>7 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>11 mg</td>
</tr>
<tr>
<td>Males</td>
<td>&lt;14 years</td>
<td>15 mg</td>
</tr>
<tr>
<td>Females</td>
<td>&gt;14 years</td>
<td>15 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>15 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 50 years</td>
<td>15 mg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2011)
* As a tocopherol adequate intake (AI)

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.
Vitamin K

Synonyms:
Phylloquinone (vitamin K1); MK-n,
Menaquinone (vitamin K2).

Chemistry:
Compounds with vitamin K activity are 3-substituted 2-methyl-1,4-
naphthoquinones. Phylloquinone contains a phytyl group, whereas
menaquinones contain a polyisoprenyl side chain with 6 to 13 isoprenyl units
at the 3-position.

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>µg/100g</th>
<th>µg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinach</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>Brussels sprouts</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>Broccoli</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Rape seed oil</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Soya bean oil</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>Lettuce</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>Cabbage</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Asparagus</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Olive oil</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Butter</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Main functions:
• Coenzyme for a vitamin K-dependent carboxylase
• Blood coagulation
• Bone metabolism

For scientific sources, please contact info.nutritionscience@dsrn.com.

Vitamin K

Fat-soluble vitamin K plays an essential role in blood clotting and is also
important for healthy bone growth and development. Vitamin K deficiency
is uncommon in healthy adults as it is widespread in foods, including dairy.
However, where vitamin K status is low, studies have shown that it can lead
to higher risk of diseases, such as osteoporosis i.e. age-related bone loss.
Functions
Vitamin K is essential for the synthesis of the biologically active forms of vitamin K-dependent proteins. It participates in the conversion of glutamate residues of these proteins to γ-carboxylglutamate residues by adding a carboxyl-group (carboxylation).

In the absence of vitamin K, carboxylation of these proteins is incomplete, and they are secreted in plasma in various so-called under-carboxylated forms, which are biologically inactive. Vitamin K is also essential for the functioning of several proteins involved in blood coagulation (clotting), a mechanism that prevents fatal bleeding from cuts and wounds, as well as internal bleeding.

Vitamin K-dependent proteins
Prothrombin (factor II), factors VII, IX, and X, and proteins C, S and Z are involved in the regulation of blood coagulation as they are synthesized in the liver. Protein S has also been detected in bone but its role in bone metabolism is not clear. The vitamin K-dependent proteins osteocalcin and matrix Gla-protein (MGP) have also been found in bone. Osteocalcin is thought to be related to bone mineralization, while MGP is present in bone, cartilage and vessel walls and has recently been established as an inhibitor of calcification.

Dietary sources
A typical western diet provides 90 percent Phylloquinone (vitamin K1) and 10 percent Menaquinone (MK-n, vitamin K2).

Phylloquinone
Rich food sources are green leafy vegetables, such as spinach, broccoli, Brussels sprouts, cabbage and lettuce.

Menaquinone
Bacterial by-product in dairy products. High MK-7 content is found in Natto (fermented soy beans, a traditional Japanese food) (0.8 - 1g/100g).

Absorption and body stores
Vitamin K is absorbed from the jejunum and ileum. As with other fat-soluble vitamins, absorption depends on the presence of bile and pancreatic juices and is enhanced by dietary fat. While the liver is the main storage site, vitamin K is also found in extrahepatic tissues, such as bone and the heart. Liver stores consist of about 10 percent phylloquinones and 90 percent menaquinones. Compared with that of other fat-soluble vitamins, the total body pool of vitamin K is small and turnover of vitamin K in the liver is rapid. The body recycles vitamin K in a process called the vitamin K cycle, allowing the vitamin to function in the γ-carboxylation of proteins. Although the liver contains menaquinones synthesized by intestinal bacteria, the absorption of menaquinones and their contribution to the human vitamin K requirement have not yet been fully elucidated.

Measurement
Plasma vitamin K concentration is measured by high performance liquid chromatography. The normal range of plasma vitamin K in adults is 0.2 - 3.2ng/ml. Levels below 0.5 ng/ml have been associated with impaired blood clotting functions. However, measuring plasma vitamin K concentrations is of limited use as it responds to changes in dietary intake within 24 hours. As vitamin K deficiency results in impaired blood clotting, laboratory tests measure clotting time. Furthermore, the plasma concentration of vitamin-K-dependent blood-clotting-factors, such as prothrombin, factor VII, factor IX, or factor X, are measured to assess inadequate vitamin K intake or vitamin K status.

Stability
Vitamin K compounds are moderately stable to heat and reducing agents but are sensitive to acid, alkali, light and oxidizing agents.

Physiological interactions
- Coumarin anticoagulants such as warfarin, salicylates and certain antibiotics act as vitamin K antagonists
- Very high dietary or supplemental intakes of vitamin K may inhibit the anticoagulant effect of vitamin K antagonists, such as warfarin
- High doses of vitamins A and E have been shown to interfere with vitamin K and precipitate deficiency states
- Absorption of vitamin K may be decreased by mineral oil, bile acid sequestrants (cholestyramine, colestipol) and orlistat (weight loss medication)

Deficiency
Vitamin K deficiency is uncommon in healthy adults but occurs in individuals with gastrointestinal disorders, fat malabsorption, liver disease or after prolonged antibiotic therapy coupled with compromised dietary intake. Impaired blood clotting is the clinical symptom of vitamin K deficiency, which is demonstrated by measuring clotting time. In severe cases, bleeding occurs. Adults at risk of vitamin K deficiency also include patients taking anticoagulant drugs, which are vitamin K antagonists.

Groups at risk
- Individuals with gastrointestinal disorders, fat malabsorption, liver disease and patients of prolonged antibiotic therapy coupled with compromised dietary intake
- Patients taking oral anticoagulant drugs, which are vitamin K antagonists
- Newborn infants can have a risk of vitamin K deficiency, which may result in fatal intracranial hemorrhage (bleeding within the skull) in the first weeks of life
- Breast-fed infants have a low vitamin K status because placental transfer of vitamin K is poor and human milk contains low levels
Reducing disease risk: therapeutic use
Phylloquinone is the preferred form of the vitamin for clinical use. It is used for intravenous and intramuscular injections as a colloid suspension, emulsion or aqueous suspension, and as a tablet for oral use.

Vitamin K1 is used in the treatment of hypoprothrombinaemia (low amounts of prothrombin), secondary to factors limiting absorption or synthesis of vitamin K. Vitamin K1 is also administered during operations in which bleeding is expected to be a problem, such as in gill-bladder surgery.

Anticoagulants prevent vitamin K recycling; however, this can be corrected rapidly and effectively by the administration of vitamin K1. Furthermore, it is often given to mothers before delivery and to newborn infants to protect against intracranial hemorrhage. A putative role of vitamin K in osteoporosis has also been investigated since vitamin K-dependent proteins may have antitumor activity and inhibit the development of metastases.

Recommended Daily Intake (RDI)
The US Food and Nutrition Board of the Institute of Medicine (2001) has established an AI level for adults, based on reported dietary intakes of vitamin K in apparently healthy population groups. Other health authorities have come to similar conclusions.

European health authorities set the AI levels for phylloquinone at 70micrograms (mcg)/day for all adults. In Germany, Austria and Switzerland, an intake of 70mcg vitamin K per day for men and 60mcg per day for women has been recommended. In the United States, an AI level for adults of 100micrograms (mcg) vitamin K per day for men and 90mcg/day for women has been established.

Safety
Even when large amounts of vitamin K1 and K2 are ingested over an extended period, toxic manifestations have not been observed. Therefore, the major health authorities have not established a tolerable UL for vitamin K. However, some allergic reactions have been reported. Administered menadione (K3) has been known to cause hemolytic anemia, jaundice and kernicterus (a grave form of jaundice in the newborn) and is no longer used for treatment of vitamin K deficiency.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>2 µg</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>2.5 µg</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>30 µg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>55 µg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>60 µg</td>
</tr>
<tr>
<td>Children</td>
<td>14 – 18 years</td>
<td>75 µg</td>
</tr>
<tr>
<td>Males</td>
<td>&gt;19 years</td>
<td>120 µg</td>
</tr>
<tr>
<td>Females</td>
<td>&gt;19 years</td>
<td>90 µg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>a</td>
<td>75 µg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>&gt;19 years</td>
<td>90 µg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>&lt;18 years</td>
<td>75 µg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>&gt;19 years</td>
<td>90 µg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2001)
** Adequate intake (AI)
Allowable levels of nutrients vary depending on national regulations and the final application.

Supplements and food fortification
Vitamin K supplements are available in tablets and capsules as well as multivitamin preparations. Infant formula products, beverages and cookies are commonly fortified with vitamin K. Menadione salts are generally preferred for farm animals because of their stability.

Production
The procedure involves the use of monooester, menadiol and an acid catalyst. Purification of the desired product, to remove unreacted reagents and side products, occurs either at the quinol stage or after oxidation.

Recommended Daily Intake (RDI)
Vitamin C

Also known as ascorbic acid, vitamin C is a water-soluble vitamin that has several important functions including the protection of cells, maintaining healthy skin, blood vessels, bones and cartilage and wound healing, as well as supporting immunity. While most animals are able to synthesize vitamin C in the body, humans do not have the ability to make their own and must obtain it via the diet alone. Oranges and orange juice, as well as other fruits and vegetables, are considered a good source of vitamin C.

Synonyms:
L-(+)-Ascorbic Acid, E300 ascorbic acid, E301 sodium ascorbate, C6H8O6, E302 calcium ascorbate, E303 potassium ascorbate, E304 fatty acid esters of ascorbic acid ((i) ascorbyl palmitate, (ii) ascorbyl stearate).

Chemistry:
L-ascorbic acid (2,3-endiol-L-gulonic acid-γ-lactone), dehydro-L-ascorbic acid (3-oxo-L-gulonic acid-γ-lactone).

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose hip</td>
<td>2000</td>
</tr>
<tr>
<td>Acerolas</td>
<td>1600</td>
</tr>
<tr>
<td>Blackcurrants</td>
<td>200</td>
</tr>
<tr>
<td>Peppers</td>
<td>128</td>
</tr>
<tr>
<td>Broccoli</td>
<td>115</td>
</tr>
<tr>
<td>Fennel</td>
<td>95</td>
</tr>
<tr>
<td>Kiwis</td>
<td>71</td>
</tr>
<tr>
<td>Strawberries</td>
<td>64</td>
</tr>
<tr>
<td>Oranges</td>
<td>49</td>
</tr>
</tbody>
</table>

Main functions:
• Antioxidant
• Immune stimulation
• Anti-allergic
• Collagen synthesis ‘cement’ for connective tissues
• Wound healing
• Teeth and gum health
• Regeneration of vitamin E
• Aids iron absorption
• Eye health

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
The most prominent role of vitamin C is its immune stimulating effect, which is important for the defense against infections such as the common cold. It also acts as an inhibitor of histamine, a compound that is released during allergic reactions. As a powerful antioxidant it can neutralize harmful free radicals and aids in neutralizing pollutants and toxins. This prevents the formation of potentially carcinogenic nitrosamines in the stomach, which mostly stem from the consumption of nitrite-containing foods, such as smoked meat. The reduction of oxidative stress has an impact on cardiovascular disease (CVD), as individuals experiencing oxidative stress have ascorbic acid blood levels lower than healthy individuals. Furthermore, vitamin C is also able to regenerate other antioxidants such as vitamin E.

As an enzyme co-factor, vitamin C is required for the synthesis of collagen, the intercellular ‘cement’ substance that gives structure to muscles, vascular tissues, bones, tendons and ligaments. Due to these functions, vitamin C, especially in combination with zinc, is important for the healing of wounds. It also contributes to the health of teeth and gums, preventing hemorrhaging and bleeding. Additionally, it improves the absorption of iron and is needed for the metabolism of bile acids, which may have implications for blood cholesterol levels and gallstones. Vitamin C plays an important role in the synthesis of several peptide hormones, neurotransmitters and carotinoids as well. Finally, vitamin C is a crucial factor in the body’s ability to deal with oxidative stress and can delay the progression of advanced age-related macular degeneration (AMD) and vision loss in combination with other antioxidant vitamins and zinc.

Dietary sources
Vitamin C is widely found in fruits and vegetables. Citrus fruits, peppers, green vegetables such as broccoli and Brussel sprouts, and fruits like strawberries, blackcurrants, guava, mango and kiwi are particularly rich sources. For example, depending on the season, one glass of fresh orange juice (100 g) yields between 15 mg and 35 mg of vitamin C. Potatoes, cabbage, spinach and tomatoes are also important sources to help meet essential vitamin C requirements.

Absorption and body stores
Intestinal absorption of vitamin C depends on the amount of dietary intake as it decreases with higher intake levels. For example, when consuming 30 to 180 mg, about 70 to 90 % is absorbed. In a single dose of 1 to 3.5g, this amounts to 50 % and in a single dose of 12 g to 16 % . Up to 500 mg can be absorbed via a sodium-dependent active transport process, while at higher doses, simple diffusion occurs. The storage capacity of water-soluble vitamins is generally low compared to that of fat-soluble ones. Humans have an average tissue store of 20 mg vitamin C per/kg body weight. The highest concentration is found in the pituitary gland (400 mg/kg). Other tissues of high concentration are the adrenal glands, eye lenses, brain, liver and white blood cells (especially lymphocytes and leukocytes).

Measurement
Vitamin C can be measured in the blood plasma and other body tissues by various techniques. Dipstick tests to estimate vitamin C levels in the urine are also available. Less satisfying the evaluation of analytical data concerning the true reflection of the body status. Threshold values are difficult to define and the subject of controversial discussion. Typical blood plasma levels are in the range of 20 to 100 µmol/L.

Influence of storage and preparation on vitamin C loss in foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Storage/preparation</th>
<th>Vitamin C loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes</td>
<td>1 month</td>
<td>50%</td>
</tr>
<tr>
<td>Fruits</td>
<td>1 month</td>
<td>20%</td>
</tr>
<tr>
<td>Apples</td>
<td>6 – 9 months</td>
<td>100%</td>
</tr>
<tr>
<td>Milk</td>
<td>UHT</td>
<td>25%</td>
</tr>
<tr>
<td>Fruits</td>
<td>Sterilization</td>
<td>50%</td>
</tr>
<tr>
<td>Fruits</td>
<td>Air drying</td>
<td>50 – 70%</td>
</tr>
<tr>
<td></td>
<td>Canning</td>
<td>48%</td>
</tr>
</tbody>
</table>

Modified from Oberheil, Fit durch Vitamine, Die neuen Wunderwaffen, Südwest Verlag GmbH & Co. KG, München 1993

Physiological interactions
• The presence of other antioxidants, such as vitamin E and β-Carotene, supports the protective antioxidant action of vitamin C. Other vitamins, such as B-complex vitamins (particularly B6, B12, folate and pantothenic acid) and some pharmacologically active substances, as well as the naturally occurring compounds known as bioflavonoids, may have a sparing effect on vitamin C i.e. vitamin C is freed up to fulfill other biological functions in the body.
• Due to toxic compounds in smoke, the vitamin C requirement for smokers and passive smokers is about 35 mg/day higher than for non-smokers. Several pharmacologically active compounds, including antidepressants, diuretics, birth control pills and aspirin (acetylsalicylic acid), deplete the tissues of vitamin C. This is also true for other habits, such as alcohol consumption and smoking.

Deficiency
Early symptoms of vitamin C deficiency are not very specific and could also indicate other diseases. Common symptoms include fatigue, lassitude, loss of appetite, drowsiness, insomnia, feeling rundown, irritability, low resistance to infections and petechiae (minor capillary bleeding). Severe vitamin C deficiency leads to scurvy, characterized by weakening of collagenous structures which results in widespread capillary bleeding. Infantine scurry also causes bone malformations. Usually, bleeding gums and loosening of the teeth are the earliest signs of clinical deficiency. Furthermore, hemorrhages under the skin can form and cause extreme tenderness of extremities and pain during movement. If left untreated, these symptoms can result in gangrene and in extreme cases, loss of life, although this rarely occurs in developed countries today. In 2013, European Food Safety Authority (EFSA) stated that the average requirement to keep bodily vitamin C at healthy levels is an intake of 90 mg/day for men and 80 mg/day for women.

Groups at risk
• Smokers and passive smokers are at a higher risk due to increased oxidative stress and metabolic turnover of vitamin C.
• People suffering from illness (i.e. cancer, stroke or tinnitus), infectious and inflammatory diseases, allergies, arteriosclerosis, high blood pressure.
• Mentally and physically stressed people.
• Pregnant and breast-feeding women.

Reducing disease risk: therapeutic use
Studies suggest that vitamin C plays a role in reducing the risk of health implications, with a selection presented below:

CVD (heart disease and stroke)
The data for vitamin C’s protective benefits against CVD are inconsistent. While some studies have failed to find significant reductions in the risk of coronary heart disease (CHD), numerous prospective cohort studies have found inverse associations between dietary vitamin C intake or vitamin C plasma levels and CVD risk. Vitamin C may protect coronary arteries by reducing the build-up of plaque, as this helps to prevent the oxidation of LDL cholesterol (the ‘bad’ cholesterol), especially in combination with vitamin E. Some data has also shown that vitamin C may boost blood levels of HDL cholesterol (the ‘good’ cholesterol), which can prevent heart disease. The risk of a stroke may be reduced by an AI of vitamin C through fruits, vegetables and supplements. However, due to the inconsistency of the data and its lack of specificity to vitamin C, the interpretation of these results is difficult.

Cancer
The role of vitamin C and cancer has been studied extensively. A number of studies have associated higher intakes of vitamin C with a decreased likeness of cancers of the upper digestive tract, cervix, ovary, bladder, and colon. Studies have also found a potential cancer-risk reduction after vitamin C supplementation has been used in cases of severe colds. This may be due to the antihistaminic action of very large doses of vitamin C.

Wound healing
During a postoperative period or during the healing process of superficial wounds, supplemental vitamin C contributes to the risk reduction of infections and promotes skin repair.

Blood pressure
Several studies have shown associated lower blood pressure levels with vitamin C supplementation at about 500 mg per day due to improved dilation of blood vessels.
day for women, based primarily on the prevention of deficiency values for vitamin C upward to 90 mg/day for men and 75 mg/day for pregnant women and breastfeeding women (115-120 mg/day).

Safety
Current recommendations state that doses above 2 g per day should be avoided to prevent side effects, including bloating and osmotic diarrhea. While the EFSA has decided that there is insufficient data to establish a tolerable upper intake level for vitamin C, one has been set by the U.S. Food and Nutrition Board in order to prevent most adults from experiencing diarrhea and disturbances in the digestive tract. Although a number of possible problems with very large doses of vitamin C have been suggested, none of these adverse health effects have been confirmed, and there is no reliable scientific evidence that large amounts of vitamin C (up to 10 g/day in adults) are toxic.

Supplements, food fortification and other applications
Vitamin C is offered in conventional, effervescent, chewable and time-release tablets, syrups, powders, granules, capsules, drops and ampoules, either alone or in multivitamin-mineral preparations. Buffered vitamin C forms i.e. highly absorbable vitamin C combined with minerals, are less acidic and allow higher doses to be administered without stomach upset. Vitamin C can also be used in the form of injections and various fruit juices, fruit-flavor drinks and breakfast cereals are enriched with vitamin C as well. On average, vitamin C supplements provide up to 8.3 % of the total vitamin C intake in Europe.

Uses in food technology
The food industry uses ascorbic acid as a natural antioxidant. Vitamin C is offered in conventional, effervescent, chewable and time-release tablets, syrups, powders, granules, capsules, drops and ampoules, either alone or in multivitamin-mineral preparations. Buffered vitamin C forms i.e. highly absorbable vitamin C combined with minerals, are less acidic and allow higher doses to be administered without stomach upset. Vitamin C can also be used in the form of injections and various fruit juices, fruit-flavor drinks and breakfast cereals are enriched with vitamin C as well. On average, vitamin C supplements provide up to 8.3 % of the total vitamin C intake in Europe.

Recommended Daily Intake (RDI)
The recommended daily intake of vitamin C varies according to age, sex, risk group and criteria applied in individual countries. In 2000, the US Food and Nutrition Board revised the RDI values for vitamin C upward to 90 mg/day for men and 75 mg/day for women, based primarily on the prevention of deficiency disease, rather than the prevention of chronic disease and the promotion of optimum health. For smokers, these RDIs are increased by an additional 35 mg/day as smokers are under increased oxidative stress from the toxins in cigarette smoke and generally have lower blood levels of vitamin C. Higher amounts of vitamin C are also recommended for pregnant (80-85 mg/day) and breastfeeding women (115-120 mg/day).

History

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0 – 6 months</td>
<td>40 mg (AI)</td>
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<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>50 mg (AI)</td>
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<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>15 mg</td>
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<td>Children</td>
<td>4 – 8 years</td>
<td>25 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>45 mg</td>
</tr>
<tr>
<td>Males</td>
<td>16 – 18 years</td>
<td>75 mg</td>
</tr>
<tr>
<td>Females</td>
<td>16 – 18 years</td>
<td>65 mg</td>
</tr>
<tr>
<td>Males &gt;19 years</td>
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<td>90 mg</td>
</tr>
<tr>
<td>Females &gt;19 years</td>
<td>19 years</td>
<td>75 mg</td>
</tr>
<tr>
<td>Smokers, male</td>
<td>19 years</td>
<td>125 mg</td>
</tr>
<tr>
<td>Smokers, female</td>
<td>19 years</td>
<td>110 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>19 years</td>
<td>60 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>19 years</td>
<td>85 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>19 years</td>
<td>115 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>19 years</td>
<td>120 mg</td>
</tr>
</tbody>
</table>

** Adequate intake (AI)
If not otherwise specified, this table presents Recommended Dietary Allowances (RDAs). Allowable levels of nutrients vary depending on national regulations and the final application.

* Institute of Medicine (2011)

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Pauling draws worldwide attention with his controversial bestseller ‘Vitamin C and the Common Cold’.

Packer and team observe the free radical interaction of vitamin E and vitamin C.

The National Cancer Institute (US) recognizes the inverse relationship between vitamin C intake and various forms of cancer, and issues guidelines for vitamin C intake.

A systematic review of thirty studies, addressing the effect of supplemented vitamin C on the duration of colds, reveals that there is a consistent benefit, which is an 8% to 14% reduction in duration.

Levine calls for a re-evaluation of vitamin C, intravenous vitamin C in particular, as part of cancer therapy.

A 5-year-long Japanese study shows that the risk of contracting three or more colds during this period was decreased by 66% with daily intake of a 500 mg vitamin C supplement.

In independent efforts, Haworth and King establish the chemical structure of vitamin C.

The synthesis of ascorbic acid was achieved by Reichstein in 1933 and industrial production began five years later by Hoffman La Roche Ltd. The vitamin division, now called DSM Nutritional Products Ltd, produces synthetic vitamin C, identical to that occurring in nature, from glucose on an industrial scale by chemical and biotechnological synthesis.

In a self-experiment, Canden proves the mandatory contribution of vitamin C in wound healing.

In 1988, Sandwich Limited, a British company, produces the first food-grade ascorbic acid identical to natural vitamin C. This is the first step towards the vitamin’s industrial production in 1989.

The relationship between vitamin C and the anti-scorbutic factor is discovered by Szent-Györgyi and at the same time by King and Waugh.

Szent-Györgyi demonstrates that the hexuronic acid he first isolated from the adrenal glands of pigs in 1928 is identical to vitamin C.

In 1932, Szent-Györgyi and Waugh. Three studies show that supplementation with vitamin C can dramatically lower lead levels.

Niki demonstrates the regeneration of vitamin E by vitamin C in model reactions.

Three studies show that supplementation with vitamin C can dramatically lower lead levels.

A bioassay is developed by Chick and Hume to determine the anti-scorbutic properties of foods.

Hippocrates describes the symptoms of scurvy.

British naval physician James Lind prescribes oranges and lemons as a cure for scurvy.

Scurvy is experimentally produced in guinea pigs by Hoot and Frolich.

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Vitamin B1 (Thiamine)

Vitamin B1, or thiamine, is one of the eight known water-soluble B vitamins. It helps to break down and release energy from food, maintain a healthy nervous system and also synthesize DNA. Deficiency of the vitamin is rare, as it can be found in most foods in small amounts, however, marginal deficiencies can lead to beriberi. In some cases, individuals take thiamine to maintain a positive mental attitude, enhance learning, increase energy and prevent memory loss.

**Synonyms:**
Antineuritic factor, nerve vitamin.

**Chemistry:**
Pyrimidine and thiazole moiety linked by a methylene bridge—phosphorylated forms: thiamine monophosphate (TMP), thiamine diphosphate (TDP), thiamine triphosphate (TTP).

**Food:**

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer's yeast</td>
<td>12</td>
</tr>
<tr>
<td>Wheat germ</td>
<td>2</td>
</tr>
<tr>
<td>Sunflower seeds</td>
<td>1.5</td>
</tr>
<tr>
<td>Brazil nuts</td>
<td>1</td>
</tr>
<tr>
<td>Pork Beans</td>
<td>0.9</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>0.8</td>
</tr>
<tr>
<td>Beef</td>
<td>0.59</td>
</tr>
</tbody>
</table>

(Source: Fachmann, Kraut)

**Molecular formula of thiamine**

**Main functions:**
- Co-enzyme in energy metabolism
- Co-enzyme for pentose metabolism as a basis for nucleic acids
- Nerve impulse conduction and muscle action

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
The main functions of thiamine are connected to its role as a coenzyme in the form of thiamine pyrophosphate (TPP). Coenzymes are ‘helper molecules’ which activate enzymes, the proteins that control the thousands of biochemical processes occurring in the human body. TPP acts as a ‘helper molecule’ in about 25 enzymatic reactions and is essential in the production of energy from food. Furthermore, TPP is a coenzyme for the metabolism of branched-chain keto acids that are derived from branched-chain amino acids.

Another important function of thiamine is its activation of an enzyme called ‘transketolase’, which in turn, catalyzes reactions in the pentose phosphate pathway. This pathway is the baseline for the production of many prominent compounds, such as ATP, GTP, NADP and the nucleic acids DNA and RNA. Certain non-coenzyme functions of thiamine are important for nerve tissues and muscles; thiamine pyrophosphate plays a role in the conduction of nerve impulses in the metabolism of neurotransmitters.

Dietary sources
Low levels of thiamine are found in most foods with the best source being dried brewer’s yeast. Other good sources include meat, especially pork and ham products, some species of fish, such as eel and tuna, whole grain cereals and bread, nuts, pulses, dried legumes and potatoes. As the thiamine-rich bran is removed during the milling of wheat and during the polishing of brown rice, many grain products, including flour and white rice, are enriched and fortified with thiamine.

Absorption and body stores
Gastrointestinal absorption of nutritional thiamine occurs in the lumen of the small intestine (mainly the jejunum) through a sodium and energy dependent active transport mechanism. For thiamine levels higher than 2 µmol/L, passive diffusion plays an additional role. Thiamine occurs in the human body as free thiamine and its phosphorylated forms. Thiamine has a high turnover rate (10 – 20 days) and is not appreciably stored in the body (approximately 1 mg/day is used up in tissues) so a daily supply is required. The limited stores may also be depleted within two weeks or less on a thiamine-free diet, with clinical signs of deficiency beginning shortly after. Regular intake of thiamine is therefore critical. The heart, kidney, liver and brain have the highest concentrations, followed by the leukocytes and red blood cells. Excess thiamine and its acid metabolites are excreted principally in the urine.

Measurement
The standard way to assess thiamine status used to be to determine erythrocyte transketolase (α-EKT) activity, both with and without stimulation of this enzyme by the addition of TDP cofactor. Technical difficulties led to an increased use of direct determination of TDP in whole blood, for example by High Performance Liquid Chromatography (HPLC). The HPLC assay is more robust and easier to perform. Thiamine status determined through this method is also considered to be in good correlation with results from transketolase activation assays. Usually, whole blood concentrations are found to be between 66.5 and 200 nmol/L.

Stability
Thiamine is unstable when exposed to heat, alkali, oxygen and radiation. Water solubility also affects the loss of thiamine from foods. In fact, about 25 % of the thiamine in food is lost during the normal cooking process. Considerable amounts may also be lost in thaw drip from frozen meats. To preserve thiamine, foods should be cooked in a covered pan for the shortest time possible and should not be soaked in water. Additionally, juices and cooking water should be re-used in stews and sauces.

Physiological interactions
- Magnesium: necessary for the conversion of thiamine to its active form
- Vitamins F and C prevent its oxidation to an inactive form
- The catalytic mechanism of pyruvate dehydrogenase and other enzymes requires the interplay of several vitamin-derived cofactors
- Smoking, sulfonamide and estrogen may raise requirements
- Alcohol reduces thiamine absorption and blocks phosphorylation of thiamine to its cofactor form (TPP)
- Drugs that cause nausea and lack of appetite, or which increase intestinal function or urinary excretion, decrease the availability of thiamine
- Digoxin, indomethacin, anticonvulsants, antacids and some diuretics may lead to the risk of deficiency
- Coffee and tea may act as antagonists
- Thiamine is degraded by thiaminases (present in raw fish and shellfish)

Deficiency
Vitamin B1 deficiency affects the cardiovascular, nervous, muscular, and gastrointestinal systems and may manifest itself in the form of fatigue, insomnia, irritability and lack of concentration, anorexia, abdominal discomfort, constipation and loss of appetite. Without enough thiamine, the overall decrease in the carbohydrate metabolism and its interconnection with the amino acid metabolism has severe consequences. The two principal thiamine deficiency diseases are ‘beriberi’ and ‘Wernicke-Korsakoff syndrome’.

Beriberi manifests itself primarily in disorders of the nervous and cardiovascular systems. While it is still common in parts of south-east Asia, where polished rice is a staple food but thiamine enrichment programs are not fully in place, many other countries fortify rice and other cereal grains to replace the nutrients lost in processing.

Beriberi exists in three forms:
- **Dry beriberi** – a polyneuropathy with severe muscle wasting
- **Wet beriberi** – which in addition to neurologic symptoms, is characterized by cardiovascular manifestations, edema and ultimately heart failure
- **Infantile beriberi** –occurs in breast-fed infants whose nursing mothers are deficient in thiamine. Symptoms, including vomiting, convulsions, abdominal distention and anorexia, usually appear quite suddenly and may be fatal in the event of heart failure

The ‘Wernicke-Korsakoff syndrome’ (cerebral beriberi) is the thiamine deficiency disease seen most often in the Western world. It is frequently associated with chronic alcoholism and in conjunction with limited food consumption. Symptoms include confusion, paralysis of eye motor nerves, abnormal oscillation of the eyes, psychosis, confabulation, and impaired retentive memory and cognitive function. The syndrome is also seen occasionally in people who fast, have chronic vomiting (hook worm) or have gross malnutrition due to diseases such as AIDS or stomach cancer. If treatment of amnesic symptoms is delayed, the memory may be permanently impaired. Recent evidence suggests that oxidative stress plays an important role in the neurologic pathology of thiamine deficiency as well.

Groups at risk
- Individuals on diuretic medication (water tablets) or digoxin (a drug used in heart failure)
- Patients recovering from heart failure
- Those suffering from or recovering from infections
- Individuals with stomach disease and those with cancer, liver or thyroid disease
- Chronic alcoholics

A ‘certain, very troublesome affliction, which attacks men, is called by the inhabitants Beriberi (which means sheep). I believe those, whom this same disease attacks, with their knees shaking and legs raised up, walk like sheep. It is a kind of paralysis, or rather Tremor: for it penetrates the motion and sensation of the hands and feet indeed sometimes the whole body…’

Jacobus Bonitus, Java, 1630
The development of thiamine deficiency can be caused by:

- Alcoholic disease
- Inadequate storage and preparation of food
- Increased demand due to pregnancy and breastfeeding, heavy physical exertion, fever and stress, or adolescent growth
- Inadequate nutrition
  - High carbohydrate intake (e.g., milled or polished rice)
  - Regular heavy consumption of tea and coffee (Tannin = anti-thiamine)
- Foods such as raw fish or betel nuts (thiaminases)
- Certain diseases (dysentery, diarrhea, cancer, nausea/vomiting, liver diseases, infections, malaria, AIDS, hyperthyroidism)
- Certain drugs (birth-control pills, neuroleptics, some cancer drugs)
- Certain drugs (birth-control pills, neuroleptics, some cancer drugs)
- Long-term parenteral nutrition (e.g., highly concentrated dextrose infusions)

Reducing disease risk: therapeutic use

Thiamine is specific in the prevention and treatment of beriberi and other manifestations of thiamine deficiency (e.g., Wernicke-Korsakoff, peripheral neuritis). The dosage range is from 100 mg daily in mild deficiency states to 200 – 300 mg in severe cases. Thiamine administration is often beneficial in severe cases. Thiamine administration is often beneficial in muscle paralysis and optic neuritis. However, the response to such treatment has been variable.

Recommended Daily Intake (RDI)

Because thiamine facilitates energy utilization, estimated requirements are calculated on the basis of energy intake, which can be very much dependent on activity levels. For adults, the RDI is 0.5 mg per 1,000 kcal, which amounts to a range of 1.0 – 1.3 mg per day for women and 1.2 mg for men, based on an average caloric intake. An additional 0.5 mg per day are recommended during pregnancy and breastfeeding.

Safety

Thiamine has been found to be well tolerated in healthy people, even at very high oral doses (up to 200 mg/day). Due to its very broad safety margin for oral administration and long history of safe use, none of the official regulatory authorities have defined a safe upper limit for this vitamin. The only reaction found in humans is of the hypersensitivity type. In the vast majority of cases, however, these reactions have occurred after injection of thiamine in patients with a history of allergic responses. For parenteral administration, the doses that produced these reactions varied from 5 mg to 100 mg, though most of them occurred at the higher end of this range.

Supplements and food fortification

Thiamine is mostly formulated in combination with other B-vitamins (B-complex) or included in multivitamin supplements. Fortification of white flour, pasta, beverages and rice began in the United States during the second World War (1939 – 1945), with other countries quickly following suit. Fortification of staple foods has virtually eradicated the B-vitamin deficiency diseases in developed nations.

Production

Chemical synthesis of thiamine is a complicated process, involving some 15 – 17 different steps. Although commercial production of thiamine was first accomplished in 1937, the production did not develop on a broad scale until the 1950s, when demand rose sharply as a result of food fortification programs.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>0.2 mg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>0.9 mg</td>
</tr>
<tr>
<td>Females</td>
<td>14 – 18 years</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Males</td>
<td>&gt;18 years</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>Adults</td>
<td>&gt;59 years</td>
<td>1.1 – 1.2 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>1.4 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 50 years</td>
<td>1.4 mg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2001)
** Adequate intake (AI)

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

History

1882: Funk isolates the antiberiberi factor from rice bran and calls it a ‘vitamine’ — an amine essential for life. The name finds ready acceptance and helps to focus attention on the new concept of deficiency diseases.

1897: Jansen and Donath propose water-soluble thiamine as the antiberiberi factor.

1912: McCollum and Davis show that the symptoms of beriberi can be reproduced in chickens fed on polished rice, and that these symptoms can be prevented or cured by feeding them rice bran.

1915: The British Medical Research Council proposes thiamine as anti-beriberi factor.

1919: Takaki, surgeon general, dramatically decreases the incidence of beriberi in the Japanese navy by improving sailors’ diets.

1926: Williams, who first began experimenting with thiamine and beriberi in Manila around 1915, reports that “the sailors’ diet is no longer boring and the health of all is improved.

1936: The first commercial production of thiamine is accomplished.

1937: The production of thiamine first took place in 1936, with the first commercial production of thiamine being commercially available in 1937.

1943: Standards of identity for enriched flour are created by the US Food and Nutrition Board, requiring that thiamine, niacin, riboflavin and iron be added to white flour.

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Vitamin B2 (Riboflavin)

Vitamin B2, also known as riboflavin, is one of the most widely distributed water-soluble vitamins. A sufficient intake of riboflavin is important, as it helps the body to convert food components into energy, neutralize free radicals that can damage cells and DNA, and also convert vitamin B6 and B9 into their active forms. Ultra violet (UV) light can destroy riboflavin, so milk, eggs, rice and fortified cereals, which are good sources of the vitamin, should be stored out of direct sunlight.

Synonyms:
Riboflavine, lactoflavine, ovoflavine.

Chemistry:
7,8-dimethyl-10-(1-D-ribityl)-isoalloxazin – different redox states: flavochinon (Flcox), flavosemichinon (Fl-H), flavohydrochinon (FlredH2). Coenzyme Form(s): FMN (flavin mononucleotide, riboflavin mono-phosphate), FAD (flavin adenine dinucleotide, riboflavin adenosine diphosphate).

Food:

<table>
<thead>
<tr>
<th></th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer’s yeast</td>
<td>3.7</td>
</tr>
<tr>
<td>Pork liver</td>
<td>3.2</td>
</tr>
<tr>
<td>Chicken breast</td>
<td>0.9</td>
</tr>
<tr>
<td>Wheat germ</td>
<td>0.7</td>
</tr>
<tr>
<td>Camembert/Parmesan</td>
<td>0.6</td>
</tr>
</tbody>
</table>

(Stout, Fachmann, Kraut)

Main functions:
• Reduction-oxidation reactions
• Energy production
• Antioxidant functions
• Conversion of pyridoxine (vitamin B6) and folic acid into their active coenzyme forms
• Growth and reproduction
• Growth of skin, hair, and nails

Molecular formula of riboflavin

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
Flavin coenzymes are essential for energy production via the respiratory chain, as they act as catalysts in the transfer of electrons in numerous reduction-oxidation reactions (redox reactions). Flavin coenzymes participate in many metabolic reactions of carbohydrates, fats and proteins. Riboflavin coenzymes are also essential for the conversion of pyridoxine (vitamin B6) and folic acid into their coenzyme forms and for the transformation of tryptophan to niacin.

Riboflavin also promotes normal growth and assists in the synthesis of steroids, red blood cells, and glycogen. Furthermore, it helps to maintain the integrity of mucous membranes, skin, eyes and the nervous system, and is involved in the production of adrenalin by the adrenal glands. Riboflavin is also important for the antioxidant status within cell systems, both by itself and as part of the glutathione reductase and xanthine oxidase system. This defense system may also help defend against bacterial infections and tumor.

Dietary sources
Most plant- and animal-derived foods contain at least small quantities of riboflavin. However, there are very few natural sources rich in the vitamin.

The most important and common dietary sources are milk and milk products, lean meat, eggs and green leafy vegetables. Cereal grains, although poor sources of riboflavin, are important for those who rely on cereals as their main dietary component. Fortified cereals and bakery products supply large amounts. Animal sources of riboflavin are more readily absorbed than vegetable sources. In milk from cows, sheep and goats, at least 90% of the riboflavin is in the free form; in most other sources, the riboflavin is mainly bound to FMN or FAD. Riboflavin is distributed in all tissues, but it is not stored to any significant extent in the body. It is excreted mainly in the urine where it contributes to the yellow color. Small amounts are also excreted in sweat and bile. During breastfeeding, about 10% of absorbed riboflavin passes into the milk.

Absorption and body stores
Most dietary riboflavin is bound to a food protein such as FMN and FAD. These are released in the stomach by acidification and absorbed in the upper part of the small intestine by an active, rapid, saturable transport mechanism. The rate of absorption is proportional to intake and increases when riboflavin is ingested along with other foods. Approximately 15% is absorbed if taken alone versus 60% absorption when taken with food. Passive diffusion plays only a minor role in the physiological doses ingested in the diet. In the mucosal cells of the intestine, riboflavin is again converted to the coenzyme form (FMN). In the portal system, it is bound to plasma albumin or to other proteins, mainly immunoglobulins, and transported to the liver, where it is converted to the other coenzyme form, FAD, and bound to specific proteins as flavoproteins.

Physiological interactions

**Physiological interactions**
- Thyroxine and triiodothyronine stimulate the FMN and FAD in mammalian systems
- Anticholinergic drugs increase the absorption of riboflavin by allowing it to stay longer at absorption sites
- Impact on metabolism, absorption, utilization and storage of riboflavin e.g. by:
  - Ouabain (treatment of congestive heart failure)
  - Theophylline (muscle relaxant, diuretic, central nervous stimulant)
- Penicillin (displaces riboflavin from its binding protein, thus inhibiting transport to the central nervous system)
- Chlorpromazin (anti-psychotic drug), barbiturates and possibly tetracyclines prevent the incorporation of riboflavin into FAD
- Riboflavin impairs the antibiotic activity of streptomycin, erythromycin, tetracyclines and tetracyclines
- Caffeine, zinc, copper and iron may chelate with riboflavin and affect its absorption

Stability
Riboflavin, in its aqueous form, is degradable by light and up to 50% may be lost if foods are left out in sunlight or any UV light. Because of this light sensivity, riboflavin will rapidly disappear from milk kept in glass bottles exposed to the sun or bright daylight (50% within 2 hours). Riboflavin is stable when heated and so is not easily destroyed in the ordinary processes of cooking, but it will leach into cooking water. The Pasteurization process causes milk to lose about 20% of its riboflavin content. Alkalics such as baking soda also destroy riboflavin. Sterilization of foods by irradiation or treatment with ethylene oxide may also cause destruction of riboflavin.

Deficiency
Overt clinical symptoms of riboflavin deficiency are rarely seen in developed countries. However, the sub-clinical stage of deficiency, characterized by a change in biochemical indices, is more common. Riboflavin deficiency rarely occurs in isolation, and is usually in combination with deficiencies of other B-complex vitamins, because flavoproteins are also involved in the metabolism of other B-complex vitamins. The absorption of iron, zinc and calcium is impaired by riboflavin deficiency.

Clinically, riboflavin-deficiency affects many organs and tissues. The most prominent affects are on the skin, mucosa and eyes:
- Glossitis (magenta tongue, geographical tongue)
- Cheilosis, angular stomatitis (fissures at the corners of the mouth)
- Sore throat
- Burning of the lips, mouth, and tongue
- Inflamed mucous membranes
- Pruritus (itching)
- Seborrheic dermatitis (moist scaly skin inflammation)
- Corneal vascularization associated with sensitivity to bright light, impaired vision, itching and a feeling of grittiness in the eyes

In severe long-term deficiency, damage to nerve tissue can cause depression and hysteria. Other symptoms are normocytic and normochromic anemia, and peripheral neuropathy of the extremities (tingling, coldness and pain). Low intracellular levels of flavin coenzymes could affect mitochondrial function, oxidative stress and blood vessel dilatation, which have been associated with pre-eclampsia during pregnancy.

Groups at risk
- Individuals with inadequate food intake e.g. the elderly, chronic dieters or people with elimination diets
- Pregnant and breastfeeding women (additional demands)
- Infants and school children
- Adolescents, particularly girls
- Chronic alcoholics
- Individuals with chronic disorders (e.g. tuberculosis, diabetes) and intestinal malabsorption (e.g. mtorus Crohn’s Disease, lactose intolerance) and trauma, including burns and surgery
- Medication users (oral-contraceptives, antibiotics, tranquillizers)
- Athletes
- Newborns after phototherapy for newborn hyperbilirubinemia
Reducing disease risk: therapeutic use

Eye-related diseases
Oxidative damage of lens proteins by light may lead to the development of age-related cataracts. Riboflavin deficiency leads to decreased glutathione reductase activity, which can result in cataracts. Therefore, riboflavin is used in combination with other antioxidants, like vitamin C and carotenoids, in the prevention of age-related cataracts. Riboflavin has been used to treat corneal ulcers, photophobia and noninfective conjunctivitis in patients without any typical signs of deficiency. Most cases of riboflavin deficiency respond to daily oral doses of 5 – 10 mg.

Migraines
People suffering from migraine headaches have a modified mitochondrial oxygen metabolism. Because riboflavin plays an important role in energy production, supplemental riboflavin has been investigated to alleviate migraines. When migraine sufferers took 400 mg/day of riboflavin for 3 months, they reported significant reductions in both migraine severity and frequency.

Prevention of deficiencies in high-risk patients
Patients suffering from achlorhydria, vomiting, diarrhea, hepatic disease, or other disorders preventing absorption or utilization, should be treated parenterally. Deficiency symptoms begin to develop in 1 – 3 days, but complete resolution may take weeks.

Elevated blood pressure
A placebo controlled double-blind randomized controlled trial in cardiovascular disease (CVD) patients recently reported that riboflavin intervention at the dietary level of 1.6 mg/d resulted in a reduction of systolic blood pressure by 13 mmHg and diastolic blood pressure by almost 8 mmHg, specifically in those individuals with the MTHFR 677 TT genotype. The global distribution of individuals with two copies of MTHFR 677T is thought to range from close to 0% in Sub-Saharan Africa to 32% in Mexico.

Recommended Daily Intake (RDI)
Dietary recommendations for riboflavin exist in many countries, where mean values for adult males vary between 1.3 and 1.6 mg daily. The recommendations of the Food and Nutrition Board of the US National Research Council are based on feeding studies conducted in the 1940s, which showed that riboflavin intake of 0.55 mg or less per day results in clinical signs of deficiency after about 90 days. These data have led to the assumption that an intake of 0.6 mg per 1,000 kcal should supply the needs of healthy people.

Safety
Riboflavin is non-toxic. No cases of toxicity from ingestion of riboflavin have been reported. A harmless yellow coloration of urine occurs at high doses. The limited capacity of the gastrointestinal tract to absorb this vitamin makes any significant risk unlikely, and because riboflavin is water-soluble, excess amounts are simply excreted.

Supplements and food fortification
Riboflavin is available as oral preparations, alone, in multivitamin and vitamin B-complex preparations, and as an injectable solution. Crystalline riboflavin (E101) is poorly soluble in water, so riboflavin-5’-phosphate (E106), a more expensive but more soluble form of riboflavin, has been developed for use in liquid formulations. Riboflavin is often added to flour, bakery products and beverages to compensate for losses due to processing. It is also used to fortify milk, breakfast cereals and dietetic products. Due to its bright yellow color, riboflavin is sometimes added to other drugs or infusion solutions as a marker.

Production
Riboflavin can be produced by chemical synthesis or by fermentation processes. Chemical processes are usually refinements of the procedures developed by Kuhn and by Karrer in 1934 using xylene, D-ribose and alloxan as starting materials. Various bacteria and fungi are commercially employed to synthesize riboflavin, using cheap natural materials and industrial wastes as a growth medium.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>0.2 mg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>0.4 mg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>0.8 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>0.9 mg</td>
</tr>
<tr>
<td>Males</td>
<td>&gt;14 years</td>
<td>1.3 mg</td>
</tr>
<tr>
<td>Females</td>
<td>16 – 18 years</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Females</td>
<td>&gt;19 years</td>
<td>1.1 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>16 – 50 years</td>
<td>1.4 – 5 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>16 – 50 years</td>
<td>1.7 mg</td>
</tr>
</tbody>
</table>

* Adequate intake (AI)
** Dose/day

Recommended Daily Intake (RDI) varies depending on national regulations and the final application.
Vitamin B3 (Niacin)

Within the human body, vitamin B3 helps to release energy from the foods we eat, produce fatty acids and cholesterol, repair DNA and contribute to the stress response. Commonly known as niacin or nicotinic acid, sufficient levels of the water-soluble vitamin are typically met by eating a varied and balanced diet.

Main functions:
- Coenzymes - Nicotinamide adenine dinucleotide (NAD) and Nicotinamide adenine dinucleotide phosphate (NADP) - in redox reactions
- NAD is a substrate for non-redox reactions

Synonyms:
Pellagra-Preventive factor (PP), nicotinic acid, nicotinamide.

Chemistry:
Nicotinic acid (pyridine-3-carboxylic acid), nicotinamide (pyridine-3 carboxamide).

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veal</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver</td>
<td>1.5</td>
</tr>
<tr>
<td>Chicken</td>
<td>1.1</td>
</tr>
<tr>
<td>Beef</td>
<td>7.5</td>
</tr>
<tr>
<td>Salmon</td>
<td>7.5</td>
</tr>
<tr>
<td>Almonds</td>
<td>4.2</td>
</tr>
<tr>
<td>Peas</td>
<td>2.4</td>
</tr>
<tr>
<td>Potatoes</td>
<td>1.2</td>
</tr>
<tr>
<td>Peaches</td>
<td>0.9</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>0.5</td>
</tr>
<tr>
<td>Milk (whole)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Molecular formula of nicotinic acid

For scientific sources, please contact info.nutritionscience@dsm.com.
Functions
The coenzymes NAD and NADP are required for around 200 biological reduction-oxidation (redox) reactions. NAD is mainly involved in reactions that generate energy in tissues through the biochemical degradation of carbohydrates, fats and proteins. NAD is also required as a substrate for non-redox reactions. It is the source of adenine diphosphate (ADP)-ribose, which is transferred to proteins by different enzymes. These enzymes and their products seem to be involved in DNA replication, DNA repair, cell differentiation and cellular signal transduction. NADP is important for the reductive biosynthesis of fatty acids and cholesterol.

Dietary sources
Nicotinic acid and niacinamide occur widely in nature. Nicotinic acid is more prevalent in plants, whereas in animals, niacinamide predominates. Most of the niacin obtained from food comes from yeast, liver, poultry, lean meats, nuts and legumes. Milk and green leafy vegetables contribute lesser amounts. Specific food processing techniques, such as the treatment of corn with lime water involved in the traditional preparation of tortillas, increase the bioavailability of niacinic acid in these products. Tryptophan contributes as much as two thirds of the niacin activity required by adults in typical diets. Important food sources of tryptophan are meat, milk and eggs.

Absorption and body stores
Both the acid and amide forms of niacin are readily absorbed from the stomach and the small intestine. At low concentrations, the two forms are absorbed by a sodium-dependent facilitated diffusion and, at higher concentrations by passive diffusion. Niacin is present in the diet mainly as NAD and NADP; and niacinamide is released from the coenzyme forms by enzymes in the intestine. The main storage organ, the liver, may contain nicotinamide is released from the coenzyme forms by enzymes. NAD is present in the diet mainly as NAD and NADP, and nicotinamide predominates. Most of the niacin obtained from food comes as NAD and NADP, and nicotinamide is between 1.3 and 4.0. Recent studies suggest that the measurement of NAD and NADP concentrations and their ratio in red blood cells may be sensitive and reliable indicators for the determination of niacin status. A ratio of erythrocyte NAD to NADP <1.0 may identify subjects at risk of developing niacin deficiency. Plasma tryptophan concentration is also used for assessment of niacin status.

Stability
Both nicotinamide and nicotinic acid are stable when exposed to heat, light, air and alkali. Little loss occurs during the cooking and storage of foods.

Deficiency
Symptoms of a marginal niacin deficiency include: insomnia, loss of appetite, weight and strength loss, soreness of the tongue and mouth, indigestion, abdominal pain, burning sensations in various parts of the body, vertigo, headaches, numbness, nervousness, poor concentration, apprehension, confusion and forgetfulness.

Severe niacin deficiency leads to pellagra, a disease characterized by dermatitis, diarrhea and dementia. A pigmented rash develops symmetrically on the skin in areas exposed to sunlight. Symptoms affecting the digestive system include a bright red tongue, stomatitis, vomiting, and diarrhea. Headaches, fatigue, depression, apathy and loss of memory are neurological symptoms of pellagra. If left untreated, pellagra is fatal. Since the synthesis of NAD from tryptophan requires an adequate supply of riboflavin and vitamin B6, insufficiencies of these vitamins may also contribute to niacin deficiency.

Pellagra is rarely seen in industrialized countries, except for its occurrence in people with chronic alcoholism. In other parts of the world where maize and jowar (barley) are the major staples, pellagra persists. It also occurs in India and parts of China and Africa.

Patients with Hartnup disease, a genetic disorder, develop pellagra because their absorption of tryptophan is defective. Carcinoid syndrome may also result in pellagra as NAD synthesis is restricted.

During disease risk: therapeutic use
Niacin is specific in the treatment of glossitis, dermatitis and the mental symptoms seen in pellagra. High doses of nicotinic acid (1.5 - 4 g/day) can reduce total and low-density lipoprotein cholesterol and triacylglycerols and increase high-density lipoprotein cholesterol in patients at risk of cardiovascular disease (CVD).

There is a flush reaction to high doses of nicotinic acid, which is seen primarily with a rising blood level and may occur once a plateau level has been reached. Nicotinic acid has also been used in doses of 100 mg as a vasodilator. Type 1 diabetes mellitus results from the autoimmune destruction of insulin-secreting β-cells in the pancreas. There is evidence that nicotinamide may delay or prevent the development of diabetes. Clinical trials are in progress to investigate this effect of nicotinamide.

Recent studies suggest that human immunodeficiency virus (HIV) increases the risk of niacin deficiency. Higher intakes of niacin were associated with decreased progression rate to AIDS in an observational study of HIV-positive men. NAD is consumed as a substrate in ADP-ribose transfer reactions to proteins which play a role in DNA repair. This has created interest in the relationship between niacin and cancer.

A large case-control study found increased consumption of niacin, along with antioxidant nutrients, to be associated with decreased incidence of cancers of the mouth, throat and esophagus.

Measurement
Determination of the urinary excretion of two niacin metabolites, N-methyl-nicotinamide and N-methyl-2-pyridone-5-carboxamide, has been used to assess niacin status. Excretion of 5.8 ± 3.6 mg N-methyl-nicotinamide/24hrs and 20.0 ± 12.9 mg N-methyl-2-pyridone-5-carboxamide/24hrs are considered normal. A ratio of the two metabolites is also used for status assessment. An adequate niacin status is considered when the ratio of N-methyl-2-pyridone-5-carboxamide to N-methyl-nicotinamide is between 1.3 and 4.0. Recent studies suggest that the measurement of NAD and NADP concentrations and their ratio in red blood cells may be sensitive and reliable indicators for the determination of niacin status. A ratio of erythrocyte NAD to NADP <1.0 may identify subjects at risk of developing niacin deficiency. Plasma tryptophan concentration is also used for assessment of niacin status.

Physiological interactions
- Copper deficiency can inhibit the conversion of tryptophan to niacin. The drug penicillamine has been demonstrated to inhibit the tryptophan-to-niacin pathway in humans. The pathway from tryptophan to niacin is sensitive to a variety of nutritional alterations; inadequate iron, riboflavin, or vitamin B6 status reduces the synthesis.
- Long-term treatment of tuberculosis with isoniazid may cause niacin deficiency, because isoniazid is a niacin antagonist. Other drugs that interact with niacin metabolism may also lead to niacin deficiency, e.g. tranquillizers (diazepam) and anticonvulsants (phenytoin, phenobarbital).

Groups at risk
- Patients with Hartnup disease
- Patients with carcinoid syndrome
- Alcoholics
- Those with long-term intake of certain drugs

Reducing disease risk: therapeutic use
Niacin is specific in the treatment of glossitis, dermatitis and the mental symptoms seen in pellagra. High doses of nicotinic acid (1.5 - 4 g/day) can reduce total and low-density lipoprotein cholesterol and triacylglycerols and increase high-density lipoprotein cholesterol in patients at risk of cardiovascular disease (CVD).

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Recommended Daily Intake (RDI)

The actual daily requirement of niacin depends on the quantity of tryptophan in the diet and the efficiency of the tryptophan to niacin conversion. The conversion factor is 60 mg of tryptophan to 1 mg of niacin, which is referred to as 1 niacin equivalent (NE). This conversion factor is used for calculating both dietary contributions from tryptophan and recommended allowances of niacin. In the US, the RDI for adults is 16 mg NEs for men and 14 mg NEs for women. RDI is estimated as 6.6 mg NE per 1,000 kcal.

Safety

There is no evidence that niacin from foods causes adverse effects. Pharmacological doses of nicotinic acid exceeding 300 mg per day have been associated with a variety of side effects including nausea, diarrhea and transient flushing of the skin. Doses exceeding 2.5 g per day have been associated with hepatotoxicity, glucose intolerance, hyperglycemia, elevated blood uric acid levels, heartburn, nausea and headaches. Severe jaundice may occur, even with doses as low as 750 mg per day, and may eventually lead to irreversible liver damage.

Doses of 1.5 to 5 g/day of nicotinic acid have been associated with blurred vision and other eye problems. Tablets with a buffer and time release capsules are available to reduce flushing and gastrointestinal irritation in individuals that are sensitive to nicotinic acid. These should be used with caution, however, because a high intake of time-release niacin tablets has been linked to liver damage. The Food and Nutrition Board (1998) set the UL for niacin (nicotinic acid plus nicotinamide) at 35 mg/day. The EU Scientific Committee on Food (2002) developed different ULs for nicotinic acid and nicotinamide: the upper level (UL) for nicotinic acid has been set at 10 mg/day, for nicotinamide at 900 mg/day.

Supplements and food fortification

Single supplements of nicotinic acid are available in tablets, capsules and syrups. Multivitamin and B-complex vitamin infusions, tablets and capsules also contain nicotinamide. Niacin is used to fortify grain, including corn and bran breakfast cereals and wheat flour.

Production

Although other routes are known, most nicotinic acid is produced by oxidation of 5-ethyl-2-methylpyridine. Nicotinamide is produced via 3-methylpyridine. This compound is derived from two carbon sources, acetaldehyde and formaldehyde, or from acrolein plus ammonia. 3-methylpyridine is first oxidized to 3-cyanopyridine which, in a second stage, converts to nicotinamide by hydrolysis.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>2 mg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>4 mg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>6 mg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>8 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>12 mg</td>
</tr>
<tr>
<td>Males</td>
<td>≥14 years</td>
<td>16 mg</td>
</tr>
<tr>
<td>Females</td>
<td>≥14 years</td>
<td>14 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>18 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 50 years</td>
<td>17 mg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2011).
** As NE. 1 mg niacin = 60 mg of tryptophan; 0 – 6 months = preformed niacin (not RNI).

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

History

1775 - Huber provides the first description of nicotinic acid.
1867 - First preparation of nicotinamide by Engler.
1873 - Spies cures human pellagra using nicotinamide.
1913 - Altschul and colleagues report that high doses of nicotinic acid reduce serum cholesterol in humans.
1915 - Goldberger and Hughes demonstrate that the main absorbed form of niacin is the amide.
1928 - Elvehjem and team show the effectiveness of nicotinic acid and nicotinamide in curing canine black tongue.
1937 - Weidel describes the elemental analysis and crystalline structure of the salts and other derivatives of nicotinic acid in some detail.
1945 - The concept of niacin equivalents is proposed by Horwitt.
1955 - Goldberger demonstrates that pellagra is a dietary deficiency disease.
1961 - Turner and Hughes demonstrate that the main absorbed form of niacin is the amide.
1978 - Shapard and colleagues report that high doses of nicotine acid lower both serum cholesterol and triglycerides.
1980 - Bredehorst and colleagues show that niacin status affects the extent of ADP-ribosylation of proteins.
Vitamin B5 (Pantothenic acid)

Synonyms:
Pantothenate, pantothenol, D-pantethenol, anti-dermatosis vitamin, chick anti-pellagra factor.

Chemistry:
Pantothenic acid is composed of β-alanine and 2,4-dihydroxy-3,3-dimethylbutyric acid (pantoic acid). Acid amide-linked pantetheine consists of pantothenic acid linked to a β-mercaptoethylamine group.

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veal liver</td>
<td>7.9</td>
</tr>
<tr>
<td>Brewer’s yeast</td>
<td>7.2</td>
</tr>
<tr>
<td>Peanuts</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Main functions:

- Metabolism of carbohydrates, proteins and fats
- Energy supply from nutrients – reduced tiredness and fatigue
- Biosynthesis of essential lipids, steroids, hormones, neurotransmitters and porphyrin
- Normal mental performance
- Formation of red blood cells, as well as sex and stress-related hormones

Vitamin B5 (Pantothenic acid)

Referred to as pantothenic acid, vitamin B5 can be found throughout all living cells and in most food sources in small amounts. The water-soluble vitamin helps to produce energy by breaking down the fats and carbohydrates in food, however, it is also known to support the synthesis of fatty acids, cell membranes, neurotransmitters and hemoglobin and promote healthy skin, hair, eyes and liver. Insufficiency of the vitamin is extremely rare, however if it does occur, typical symptoms include tiredness, nausea and vomiting, numbness or ‘burning feet’.

For scientific sources, please contact info.nutritionscience@dsm.com.
and whole-grain cereals are also common sources of vitamin B5, however.

**Functions**
Pantothenic acid, as a metabolically active component of coenzyme-A (CoA) and acyl carrier protein (ACP, an enzyme involved in the synthesis of fatty acids), plays a key role in the metabolism of carbohydrates, proteins and fats, and is therefore essential for the maintenance and repair of all cells and tissues in the body. CoA is involved in a broad range of acetyl- and acyl-transfer steps and reactions of the oxidative metabolism and catabolism. Hence it is significant in helping to supply energy. For example, in the process of fat burning (metabolism and catabolism), energy is released from stored fat as acetyl-coenzyme A (CoA) and acyl-coenzyme A (ACP). CoA and ACP are also required for certain cell structures.

**Measurement**
Since vitamin B5 dietary deficiency is practically unknown, little research has been conducted to assess pantothenate status in humans. Nutritional status can be indicated from the levels of pantothenic acid in the body. Measurement of the blood levels of free pantothenic acid can be performed by radioimmunoassay and ELISA. A more thorough, sensitive approach is the use of chromatography/Mass Spectrometry and immunological methods (radioimmunoassay, ELISA) have also been applied. Since vitamin B5 dietary deficiency is practically unknown, little research has been conducted to assess pantothenate status in humans. Nutritional status can be indicated from the levels of pantothenic acid in the body. Measurement of the blood levels of free pantothenic acid can be performed by radioimmunoassay and ELISA. It has therefore been suggested that pantothenic acid utilization is impaired in alcoholics. Birth control pills containing estrogen and progesterin may increase the requirement for pantothenic acid. The most common antagonist of pantothenic acid used experimentally to accelerate the appearance of deficiency symptoms is omega-methyl pantothenic acid. This condition was reversed by pantothenic acid supplementation, of the liver to eliminate toxins (hepatic encephalopathy). This condition was reversed by pantothenic acid supplementation, suggesting it was due to pantothenic acid deficiency caused by the antagonist. Interestingly, in experiments with mice it has been shown that a deficiency of pantothenic acid leads to skin irritation and greying of the fur, which were reversed by giving pantothenic acid. Panthenol has since been added to shampoos and hair care products including shampoos and hair care products.

**Deficiency**
Since pantothenic acid occurs to some extent in all foods, it is generally assumed that dietary deficiency of this vitamin is extremely rare. However, pantothenic acid deficiency in humans is not well documented and probably does not occur in isolation, but in conjunction with deficiencies of other B vitamins. Deficiency symptoms have been produced experimentally by administering the antagonist omega-methyl pantothenic acid in addition to a pantothenic acid-deficient diet. They include fatigue, headaches, insomnia, nausea, abdominal cramps, vomiting and flatulence. The symptoms are the result of low CoA levels, impaired acetylcholine synthesis and altered carbohydrate and lipid metabolism.

Homopantothenate is a pantothenic acid antagonist that has been used in Japan to enhance mental function, especially in Alzheimer’s disease patients. However, a rare side effect of this treatment is abnormal brain function resulting from the failure of the liver to eliminate toxins (hepatic encephalopathy). This condition was reversed by pantothenic acid supplementation, suggesting it was due to pantothenic acid deficiency caused by the antagonist. Interestingly, in experiments with mice it has been shown that a deficiency of pantothenic acid leads to skin irritation and greying of the fur, which were reversed by giving pantothenic acid. Panthenol has since been added to shampoos and hair care products including shampoos and hair care products.

**Recommended daily intakes (RDI)**

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<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0 – 6 months</td>
<td>1.7 mg</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 13 years</td>
<td>1.8 – 4 mg</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14 – 18 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>Adults</td>
<td>19 – 70 years</td>
<td>5 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>6 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td>7 mg</td>
</tr>
</tbody>
</table>

* EFSA (2014)
** Adequate intake (AI)

Alcoholics and individuals with impaired absorption are considered at risk.
Reducing disease risk: therapeutic use

Although isolated deficiency states are rarely observed, several investigators have noted changes in pantothenic acid levels in patients affected by various diseases, and pharmacological amounts of the vitamin are used in the treatment of numerous conditions. In most cases, however, the claimed therapeutic response has not been confirmed by controlled studies in humans.

For the treatment of deficiency due to impaired absorption, intravenous or intramuscular injections of 500 mg are recommended several times a week. Postoperative ileus (paralysis of the intestine) requires doses of up to 1,000 mg every six hours. Panthenol is applied topically to the skin and mucosa to speed up the healing of wounds, (diabetic) ulcers and inflammation, such as cuts and grazes, burns, sunburn, nappy rash, bed sores, laryngitis and bronchitis. In combination, pantothenic acid and ascorbic acid significantly enhance the healing process.

Safety

Pantothenic acid is essentially considered to be non-toxic, and no cases of hypervitaminosis have ever been reported. A daily intake of as much as 10 g produces only minor gastrointestinal disturbance (diarrhea) in humans. Pantothenate derivatives are not mutagenic in bacterial tests, however high doses (≤ 10 – 15 g) can cause transient nausea and a lack of fatigue in humans. Due to the lack of human data detailing adverse effects, the main regulatory authorities have not defined a tolerable UL for pantothenic acid.

Supplements and food fortification

Pure pantothenic acid is a viscous hygroscopic oil that is chemically not very stable. Supplements therefore usually contain the calcium salt, or alcohol, panthenol. Both are highly water-soluble and are rapidly converted to the free acid in the body. Calcium pantothenate is often included in multivitamin preparations; panthenol is the more common form used in mono-preparations, which are available in a wide variety of pharmaceutical forms (e.g. solutions for injection and local application, aerosols, tablets, ointments and creams). Pantethine, an active form that is used as a cholesterol and triglyceride-lowering drug in Europe and Japan and is also available in the US as a dietary supplement. Pantethine is added to a variety of foods, the most important of which are breakfast cereals and beverages, as well as dietetic and baby foods.

Production

Pantothenic acid is primarily chemically synthesized by condensation of D-pantolactone with β-alanine. Addition of a calcium salt produces colorless crystals of calcium pantothenate, which have 100% purity. Furthermore, pantothenic acid can be purified through a biotechnological process. Brewer's yeast is considered a low purity natural source. Panthenol is produced as a clear, almost colorless, viscous hygroscopic liquid.

Recommended Daily Intake (RDI)

It is widely agreed that there is insufficient information available on which to base an RDI for pantothenic acid. Most countries that make recommendations therefore give an estimate of safe and adequate levels for daily intake. These DAs are based on estimated dietary intakes in healthy population groups and range from 2 to 14 mg for adults.

History

Williams and Trusdall separate an acid fraction from ‘bias’, the growth factor for yeast.

Williams and team show this fraction to be a single acid substance essential for the growth of yeast. It is found in a wide range of biological materials, so they suggest calling it ‘pantothenic acid’.

Kuhn and his team in Heidelberg, and Karrer and colleagues in Zurich, synthesize pure riboflavin.

Lipmann and his colleagues establish the structure of pantothenic acid.

1947

The full structure of CoA is elucidated by Baddiley and colleagues. Lipmann receives the Nobel Prize, together with Krebs, for his work on CoA and its role in metabolism.

1953

Bean and Hodgks report that pantothenic acid is essential in human nutrition. Subsequently, they and their colleagues conduct several further studies to produce deficiency symptoms in healthy humans using the antagonistic omega-methyl pantothenic acid.

1954

Pugh and Wakil identify the acyl carrier protein as an additional active form of pantothenic acid.

1965

Fry and team measure the metabolic response of humans to deprivation.

1976

1931

1933

1938

1940

1951

1965

1979

1976

1979

1979

1979

1979
**Vitamin B6 (Pyridoxin)**

**Synonyms:**
Vitamin B6 is composed of three forms: pyridoxine or pyridoxol (the alcohol), pyridoxal (the aldehyde) and pyridoxamine (the amine).

**Chemistry:**
Vitamin B6 is the generic term for all 2-hydroxy 2-methylpyrimidine derivatives exhibiting the biological activity of pyridoxine. Besides the alcohol pyridoxine, these compounds include the aldehyde pyridoxal and the amine pyridoxamine and their respective 5'- phosphates (PLP, PNP, and PMP). All these compounds are nutritionally equivalent and can be metabolically converted to pyridoxalphosphate (PLP) which is the only vitamin B6 compound with known functions as an enzymatic cofactor.

**Food:**

<table>
<thead>
<tr>
<th>Food</th>
<th>mg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer’s yeast</td>
<td>4.4</td>
</tr>
<tr>
<td>Salmon</td>
<td>0.98</td>
</tr>
<tr>
<td>Walnuts</td>
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<td>Wheat germ</td>
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<td>Pork liver</td>
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<td>Lentils</td>
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<tr>
<td>Avocado</td>
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<tr>
<td>Chicken</td>
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<tr>
<td>Zucchini</td>
<td>0.46</td>
</tr>
<tr>
<td>Bananas</td>
<td>0.36</td>
</tr>
</tbody>
</table>

(Source: Fachmann, Kraut)

**Main functions:**
- Neurotransmitter synthesis
- Red blood cell formation
- Niacin formation
- Degradation of homocysteine to cysteine
- Inhibition of steroid hormone signaling
- Support of immune defense

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For scientific sources, please contact info.nutritionscience@dsm.com.

One of the eight vitamins in the B vitamin group, B6 is essential in helping to convert glycogen into glucose in the body. Glucose is used to produce energy and make neurotransmitters, which carry signals from one nerve cell to the other. Vitamin B6 is also important for enzymes involved in protein metabolism and it helps to produce hormones, red blood cells and cells of the immune system. Studies show that vitamin B6 is especially important in the elderly, as this group often suffers from impaired immune function.
Absorption and body stores

All three forms of vitamin B6 (pyridoxine, pyridoxal and pyridoxamine) are readily absorbed in the small intestine by an energy-dependent process. They are all converted to pyridoxal phosphate in the liver, a process which requires zinc and riboflavin. The bioavailability of plant-based vitamin B6 varies considerably, ranging from 0% to 80%. Some plants contain pyridoxine glycosides that cannot be hydrolyzed by intestinal enzymes. Although these glycosides may be absorbed, they do not contribute to vitamin activity. The storage capacity of water-soluble vitamins is generally low compared to that of fat-soluble ones. Small quantities of pyridoxine are widely distributed in body tissue, mainly as PLP in the liver and in muscle. PLP is tightly bound to the protein’s albumin and hemoglobin in plasma and red blood cells. Because the half-life of pyridoxine is about 25 days and it is not significantly bound to plasma proteins, the limited stores may be depleted within two to six weeks on a pyridoxin-free diet. Excess pyridoxine is primarily excreted in the urine as 4-pyridoxic acid (4-PA) and, to a limited extent, in feces.

Measurement

There are several direct and indirect methods that can be used for assessing an individual’s vitamin B6 status. Direct methods include determination of PLP in plasma, and determination of urinary excretion of 4-pyridoxic acid (4-PA). The method of choice for quantification of both compounds is high-performance liquid chromatography. Whole blood concentrations usually are 35 – 110 nmol/L PLP. Concentrations of PLP have been found to correlate well with the vitamin B6 deficiency determined by indirect methods. Indirect methods measure the stimulated activity of pyridoxine-dependent enzymes in erythrocytes by addition of PLP. This mainly determines the erythrocyte alanine aminotransferase activation coefficient (EAST-AC) or the erythrocyte aspartate aminotransferase activation coefficient. The coefficient of activity with stimulation to activity without stimulation indicates the vitamin B6 status. For EAST-AC, values >1.8 are considered to show deficiency, 1.7 – 1.8 to be marginal, and <1.7 to be adequate. For large-scale population surveys, the tryptophan load test is another method of assessing vitamin B6 deficiency. Vitamin B6 participates in the conversion of tryptophan to the vitamin niacin. A vitamin B6 deficiency blocks this process, producing more xanthurenic acid. If the administration of tryptophan leads to an increased excretion of xanthurenic acid, a vitamin B6 deficiency can be diagnosed.

Stability

Pyridoxine is relatively stable to heat, but pyridoxal and pyridoxamine are not. Pasteurization therefore causes milk to lose up to 20% of its vitamin B6 content. Vitamin B6 is decomposed by oxidation, ultraviolet light and alkaline environments. Because of this light sensitivity, vitamin B6 will disappear (50% within a few hours) from milk kept in glass bottles exposed to the sun or bright daylight. Alkaloids, such as baking soda, also destroy pyridoxine. The freezing of vegetables causes a reduction of up to 20%, while milling of cereals leads to wastes as high as 90%. Cooking losses of processed foods may range from a few percent to nearly half the vitamin B6 originally present. Cooking and storage losses are greater with animal products.

Functions

PLP serves as a coenzyme of more than 60 enzymes that catalyze essential chemical reactions in the human body. It plays an important role in protein, carbohydrate and lipid metabolism. It is involved in the production of serotonin from the amino acid tryptophan in the brain and other neurotransmitters, and so it has a role in the regulation of mental processes and mood. Furthermore, it is involved in the conversion of tryptophan to the vitamin niacin, the formation of hemoglobin and the growth of red blood cells, the production of prostaglandins and hydrochloric acid in the gastrointestinal tract, the sodium-potassium balance, and in histamine metabolism. Vitamin B6 also plays a role in the improvement of the immune system.

Dietary sources

Vitamin B6 is widely distributed in foods and is mainly found in bound forms. Pyridoxine is found in plants, whereas pyridoxal and pyridoxamine are principally found in animal tissue, mainly in the form of PLP.

Rich sources of vitamin B6 include chicken and beef, pork and veal liver, fish (salmon, tuna, sardines, halibut, herring), nuts (walnuts, peanuts), brewer’s yeast, and wheat germ.

Generally, vegetables and fruits are rather poor sources of vitamin B6, although there are members of these food classes which contain considerable amounts of pyridoxine, such as lentils, zucchinis, avocados and bananas.

Physiological interactions

- Certain vitamins of the B-complex (niacin, riboflavin, biotin) may act synergistically with vitamin B6 derivatives.
- Vitamin B6 additionally requires zinc and magnesium to fulfill its physiological functions.
- There are more than 40 drugs that interfere with vitamin B6 metabolism, potentially causing low status e.g.:
  - Phenytoin (an antiepileptic drug)
  - Theophylline (a drug for respiratory diseases)
  - Phenobarbitone (a barbiturate mainly used for its antiepileptic properties)
  - Desoxyripyridoxine (a tuberculosstatic drug)
  - Hydralazine (an antihypertensive)
  - Cycloserine (an antibiotic)
- Vitamin B6 reduces the therapeutic effect of levodopa by accelerating its metabolism
- Levodopa reduces vitamin B6 status as the drug forms a Schiff base complex with PLP

Deficiency

Vitamin B6 deficiency alone is uncommon, because it usually occurs in combination with a deficit in other B-complex vitamins, especially with riboflavin, because riboflavin is needed for the formation of the coenzyme PLP. A recent diet survey revealed that a significant part of the following population groups have B6 intakes below the RDI.

Groups at risk

- The elderly are at risk due to lower food intake, increased B6 catabolism and decreased protein binding capacity
- Pregnant and breastfeeding women (additional demands)
- Women in general, especially those taking oral contraceptives
- Patients on drugs interacting with B-vitamin metabolism
- Underweight people or people who eat poorly, (e.g. people with eating disorders)
- Chronic alcoholics (heavy drinking may severely impair the ability of the liver to synthesize PLP)

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>0.1 mg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>0.3 mg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Males</td>
<td>14 – 50 years</td>
<td>1.3 mg</td>
</tr>
<tr>
<td>Females</td>
<td>14 – 18 years</td>
<td>1.2 mg</td>
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<tr>
<td>Females</td>
<td>19 – 50 years</td>
<td>1.3 mg</td>
</tr>
<tr>
<td>Males</td>
<td>≥51 years</td>
<td>1.7 mg</td>
</tr>
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<td>Females</td>
<td>≥51 years</td>
<td>1.7 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>1.9 mg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 50 years</td>
<td>2.0 mg</td>
</tr>
</tbody>
</table>

* Institute of Medicine (2001) 
** Adequate intake (AI) 
If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.
Reducing disease risk: therapeutic use
Sideroblastic anemias and pyridoxine-dependent abnormalities of metabolism

Pyridoxine is an approved treatment for sideroblastic anemias and pyridoxine-dependent abnormalities of metabolism. In such cases, therapeutic doses of approximately 40–200 mg vitamin B6 per day are indicated. Vitamin B6 deficiency is also associated with hypochromic microcytic anemia.

PMS (premenstrual syndrome)
Some studies suggest that vitamin B6 doses of up to 100 mg/day may be beneficial for relieving the symptoms of premenstrual syndrome.

Hyperemesis gravidarum
Pyridoxine is often administered in doses of up to 40 mg/day in the treatment of nausea and vomiting during pregnancy (hyperemesis gravidarum).

Depression
Pyridoxine is also used to assist in the relief of depression especially in women taking oral contraceptives. However, clinical trials have not yet provided evidence for its efficacy.

Carpal tunnel syndrome
Pyridoxine has been claimed to alleviate the symptoms of carpal tunnel syndrome.

Hyperhomocystinaemia/cardiovascular disease (CVD)
Elevated homocysteine levels in the blood are considered a risk factor for atherosclerotic disease. Several studies have shown that vitamin B6, vitamin B12 and folic acid can lower risk factor for atherosclerotic disease. Several studies have shown that vitamin B6 required to improve the immune system is higher than the current RDI (2.4 mg/day for men; 1.9 mg/day for women).

Asthma
Asthma patients taking vitamin B6 supplements may have fewer, and less severe, attacks of wheezing, coughing and breathing difficulties.

Diabetes
Research has also suggested that certain patients with diabetes mellitus or gestational diabetes experience an improvement in glucose tolerance when given vitamin B6 supplements.

Kidney stones
Glyoxylate can be oxidized to oxalic acid that may then lead to calcium oxalate kidney stones. Pyridoxal phosphate is a cofactor for the degradation of glyoxylate to glycine. There is some evidence that high doses of vitamin B6 (>150 mg/day) may be useful for normalizing the oxalic acid metabolism to reduce the formation of kidney stones. However, the relationship between B6 and kidney stones must be studied further before any definite conclusions can be drawn.

Glutamate sensitivity
People who are sensitive to glutamate, which is often used for the preparation of Asian dishes, can react with headache, tachycardia (accelerated heart rate), and nausea. 50 to 100 mg of pyridoxine can then be of therapeutic value.

Autism
High dose therapy with pyridoxine improves the status of autistics in about 30% of cases.

Recommended Daily Intake (RDI)
The recommended daily intake of vitamin B6 varies according to age, sex, risk group (see ‘Groups at risk’) and criteria applied. Vitamin B6 requirement is increased when high-protein diets are consumed, since protein metabolism can only function properly with the assistance of vitamin B6 derivatives.

Pregnant and breastfeeding women need an additional 0.7 mg to compensate for increased demands made by the fetus or baby.

Safety
Vitamin B6 in all its forms is well tolerated, but large amounts are toxic. Daily oral doses of pyridoxine of up to 50 times the RDI (ca. 100 mg) for periods of 3 – 4 years have been administered without adverse effects. Daily doses of 500 mg and more may cause sensory neuropathy after several years of ingestion, whereas the intake of amounts in excess of 1 gram daily may lead to reversible sensory neuropathy within a few months. Sensory neuropathy has been selected as a critical end-point on which to base a tolerable upper intake level (UL) of 100 mg/day (IOM). The factor is then called the rat anti-acro-dynia factor, deficiency of which causes so-called ‘rat-pellagra’.

Supplements and food fortification
The most commonly available form of vitamin B6 is pyridoxine hydrochloride, which is used in food fortification, nutritional supplements and therapeutic products such as capsules, tablets and ampoules. Vitamins, mostly of the B-complex, are widely used in the enrichment of cereals. Dietetic foods such as infant formulas and slimming diets are often fortified with vitamin B6, pyridoxine- dependent abnormalities of metabolism. In such cases, therapeutic doses of approximately 40–200 mg vitamin B6 per day are indicated. Vitamin B6 deficiency is also associated with hypochromic microcytic anemia.

Goldberger and colleagues feed rats a diet deficient in what is considered to be the pellagra-preventive factor; these animals develop skin lesions.

1926
Goldberger and colleagues succeed in differentiating riboflavin and vitamin B6 from the specific pellagra protective factor (P-P) of Goldberger and his team.

1935
Birch and György succeed in synthesizing riboflavin and vitamin B6 from the specific pellagra preventive factor (P-P) of Goldberger and his team.

1938
Lepkovsky is the first to report the isolation of pure crystalline vitamin B6 from rice polishing (Keresztesy and Stevens; György, Kuhn and Wendt; Ichiba and Michi).

1939
Snell demonstrates that two other natural forms of the vitamin exist, namely pyridoxal and pyridoxamine.

1945
Soydman determines the levels of vitamin B6 required by humans.

1957
Harris and Folkers determine the structure of pyridoxine and succeed in synthesizing the vitamin. György proposes the name pyridoxine.

1966
György first identifies this factor as vitamin B6 or adermin, a substance capable of curing a characteristic skin disease in rats (dermatitis acrodynia). The factor is then called the rat anti-acro-dynia factor, deficiency of which causes so-called ‘rat-pellagra’.

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**Vitamin B7 (Biotin)**

Biotin, or vitamin B7, is only needed in very small amounts and helps to metabolize proteins and form glucose. It can be synthesized by bacteria, molds, yeasts, algae and other plant species. Any unused biotin is eliminated in urine, so the body does not build up reserves. As such, it must be consumed daily from the diet.

**Synonyms:**
Vitamin H (‘Haar und Haut’, German words for ‘hair and skin’) and co-enzyme R.

**Chemistry:**
Biotin has a bicyclic ring structure. One ring contains a ureido group and the other contains a heterocyclic sulfur atom and a valeric acid side-group. **(Hexahydro-2-oxo-1H-thieno [3,4-] dimidazole-4-pentanoic acid).** Biologically active analogues: biocytin (**ε-N-biotinyl-L-lysine**), oxybiotin (**S** substituted with **O**).

**Food:**

<table>
<thead>
<tr>
<th>Food</th>
<th>µg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brewer’s yeast</td>
<td>115</td>
</tr>
<tr>
<td>Beef liver</td>
<td>100</td>
</tr>
<tr>
<td>Soya beans</td>
<td>60</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>45</td>
</tr>
<tr>
<td>Peanuts</td>
<td>35</td>
</tr>
<tr>
<td>Eggs</td>
<td>35</td>
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<tr>
<td>White mushrooms</td>
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<tr>
<td>Spinach</td>
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<tr>
<td>Strawberries</td>
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<tr>
<td>Whole wheat bread</td>
<td>2</td>
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<tr>
<td>Asparagus</td>
<td>2</td>
</tr>
<tr>
<td>(Souci, Fachmann, Kraut)</td>
<td></td>
</tr>
</tbody>
</table>

**Main functions:**
- Produce fatty acids and amino acids (the building blocks for protein and lipids)
- Convert food into glucose, which is used to produce energy
- Activate protein and amino acid metabolism in cells
- Maintenance of healthy hair, skin and nails

For scientific sources, please contact info.nutritionscience@dsrn.com.
Absorption and body stores
In most foods, biotin is bound to proteins from which it is released in the intestine by protein hydrolysis and a specific enzyme, biotinidase. Biotin is then absorbed unchanged in the upper part of the small intestine by an electron-neutral sodium (Na+) gradient dependent carrier-mediated process, and also by slow passive diffusion when at therapeutic doses. The carrier is regulated by the availability of biotin, with up-regulation of the number of transporter molecules when biotin is deficient. The colon is also able to absorb biotin via an analogue transport mechanism. Once absorbed, biotin is distributed to all tissues. The liver and kidney are the main storage places. Biotin metabolites are not active as vitamins and are excreted in the urine. High amounts of biotin, synthesized by colonic bacteria, also appear in feces.

Measurement
The status of biotin in the body can be determined by measuring the activity and/or activation of biotin-dependent enzymes – predominately carboxylases. More convenient methods, however, are the direct determination of biotin in plasma or serum by microbiological methods or avidin binding assays, or determination of biotin excretion and 3-hydroxyisovaleric acid in urine. Measurement of biotin in plasma is not a reliable indicator of nutritional status as reported concentrations for biotin in the blood vary widely. Thus, a low plasma-biotin concentration is not a sensitive indicator of inadequate intake. Usual serum concentrations are 100 – 400 pmol/L.

Stability
Biotin is relatively stable when heated and therefore not easily destroyed in the process of cooking, but it will filter into cooking water. The processing of food, e.g. canning, can cause a moderate reduction in biotin content.

Physiological interactions
• Raw egg whites contain avidin, a glycoprotein that strongly binds to biotin and prevents its absorption in the body. As such, the ingestion of large quantities of raw egg white over a long period can result in a biotin deficiency. It has also been reported that antibiotics, which damage the intestinal flora (thus decreasing bacterial synthesis), can also reduce biotin concentrations. Interactions with certain anticonvulsant drugs and alcohol have been reported, as they may inhibit intestinal carrier-mediated transport of biotin. Finally, pantethine acid ingested in large amounts competes with biotin for intestinal and cellular uptake because they both use the same transporter.

Deficiency
Human biotin deficiency is extremely rare. This is probably due to the fact that biotin is synthesized by beneficial bacteria in the human digestive tract. Symptoms of deficiency include hair loss, dry scaly skin, cracking lips, depression, lethargy, hallucination, numbness and tingling of the extremities, as well as ataxia.

Groups at risk
• Patients dependent on total intravenous nutrition
• Dialysis patients
• Individuals receiving some forms of long-term anticonvulsant therapy
• Individuals with biotinidase deficiency or holocarboxylase synthetase (HCS) deficiency (genetic defects)
• Patients with malabsorption, including short-bowel syndrome
• People who eat large amounts of raw egg white
• Pregnant women may experience marginal biotin deficiency

Reducing disease risk: therapeutic use
There is no direct evidence that marginal biotin deficiency causes birth defects in humans, but adequate biotin intake during pregnancy is advisable. Biotin is used clinically to treat the biotin-responsive inborn errors of metabolism, holocarboxylase synthetase deficiency and biotinidase deficiency. Large doses of biotin may be given to babies with a condition called infantile seborrhea, or to patients with genetic abnormalities in biotin metabolism. A large number of reports has shown a beneficial effect of biotin in infant seborrheic dermatitis, Leiner’s disease (a generalized form of seborrheic dermatitis) and also palmoplantar pustulosis. Individuals with type 2 diabetes often have low concentrations of biotin. In some diabetic patients, it has been advised that there may be an abnormality in the biotin-dependent enzyme pyruvate carboxylase, which can lead to dysfunction of the nervous system.

The main benefit of biotin as a dietary supplement is in strengthening hair and nails. Uncombable hair syndrome in children also improves with biotin supplementation, as do certain skin disorders, such as ‘cradle cap’.

Recommended Daily Intake (RDI)
In 1998, the Food and Nutrition Board of the Institute of Medicine felt the existing scientific evidence was insufficient to calculate an EAR, and thus an RDI, for biotin. Instead an AI level has been defined. The AI for biotin assumes that current average intakes of biotin (35 µg to 60 µg/day) are meeting the dietary requirement. The present recommended daily intake in the US is 20 – 30 µg daily for adults and children over 9 years, and 5 – 12 µg daily for infants and younger children. EFSA recommends the AI of biotin for adults and pregnant women should be set at 40 µg per day – adding an additional 5 µg daily for breastfeeding women. For infants, the amount provided by breastmilk is considered adequate, therefore for infants older than six months an AI of 6 µg per day is extrapolated from the breastmilk intake.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>5 µg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>6 µg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>8 µg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>12 µg (AI)</td>
</tr>
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<td>Children</td>
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<td>20 µg (AI)</td>
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<td>Children</td>
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<td>25 µg (AI)</td>
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<tr>
<td>Adults</td>
<td>&gt;19 years</td>
<td>30 µg (AI)</td>
</tr>
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<td>Pregnancy</td>
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</tr>
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<td>Breastfeeding</td>
<td>&gt;50 years</td>
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</tbody>
</table>

* Institute of Medicine (2007)
** Adequate intake (AI)
**Safety**

No known toxicity has been associated with biotin. Biotin has been administered in doses as high as 40 mg per day without objectionable effects. As a result, no major regulatory authorities have established a UL for biotin.

**Supplements and other applications**

Biotin, usually either in the form of crystalline D-biotin or brewer’s yeast, is added to many dietary supplements, infant milk formulas and baby foods, as well as various dietetic products. As a supplement, biotin is often included in combinations of the B vitamins. Mono-preparations of biotin are available in some countries as oral and parenteral formulations.

Therapeutic doses of biotin range between 5 and 20 mg daily. Seborrhoeic dermatitis and Leiner’s disease in infants respond to daily doses of 5 mg. Patients with biotinidase deficiency require life-long biotin therapy in milligram doses (5 – 10 mg/day). Patients with HCS deficiency require supplementation of 40 – 100 mg/day. If biotin therapy is introduced in infancy, the prognosis for both these genetic defects is good. A daily supplement of 60 µg biotin for adults and 20 µg for children has been recommended to maintain normal plasma concentrations in patients on total parenteral nutrition.

**Production**

Commercial synthesis of biotin is based on a method developed by Goldberg and Sternbach in 1949, which uses fumaric acid as starting material. This technique produces a pure D-biotin that is identical to the natural product.

**History**

- **1901** Bateman observes the detrimental effect of feeding high doses of raw egg white to animals.
- **1916** György also discovers this factor in the liver and calls it vitamin H.
- **1927** Kögl and Tönnis extract a crystalline growth factor from dried egg yolk and suggest the name ‘biotin’.
- **1931** Kögl and Tönnis prove the findings of dermatosis and hair loss in rats fed with raw egg white. She shows that this egg white injury can be cured by a protective factor X found in the liver.
- **1935** Kögl and his group in Europe, and du Vigneaud and his colleagues in the US, establish the structure of biotin.
- **1940** György and his team conclude that biotin, vitamin H and coenzyme R are identical. They also succeed in isolating biotin from the liver.
- **1942** Sydenstricker and colleagues demonstrate the need for biotin in the human diet.
- **1943** Gold and Sternbach develop a technique for the industrial production of biotin.
- **1949** Goldberg and Sternbach develop a technique for the industrial production of biotin.
- **1956** Traub confirms the structure of biotin by X-ray analysis.
- **1959** Lynen’s group describes the biological function of biotin and paves the way for further studies on the carboxylase enzymes.
- **1961** First description of an inborn error of biotin-dependent carboxylase metabolism by Gompertz and his team.
- **1963** Burri and her colleagues show that the early infantile form of multiple carboxylase deficiency is due to a mutation affecting holocarboxylase synthetase activity.
- **1981** Burri and team suggest that late-onset multiple carboxylase deficiency results from a deficiency in biotinidase activity.
- **1983** Total synthesis of biotin by Harris and colleagues in the US.
Vitamin B9 (Folic acid)

Synonyms:
Folate, folacin, folinic acid.

Chemistry:
Folic acid consists of a pteridine ring system, p-aminobenzoic acid and one molecule of glutamic acid (chemical name: pteroylglutamic acid). Naturally-occurring folates are pteroylpolyglutamic acids with two to eight glutamic acid groups.

Food:

<table>
<thead>
<tr>
<th>Food</th>
<th>µg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef liver</td>
<td>592</td>
</tr>
<tr>
<td>Peanuts</td>
<td>169</td>
</tr>
<tr>
<td>Spinach</td>
<td>145</td>
</tr>
<tr>
<td>Broccoli</td>
<td>114</td>
</tr>
<tr>
<td>Asparagus</td>
<td>108</td>
</tr>
<tr>
<td>Eggs</td>
<td>87</td>
</tr>
<tr>
<td>Strawberries</td>
<td>63</td>
</tr>
<tr>
<td>Orange juice (freshly squeezed)</td>
<td>41</td>
</tr>
<tr>
<td>Tomatoes</td>
<td>22</td>
</tr>
<tr>
<td>Milk (whole)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

For scientific sources, please contact info.nutritionscience@dsm.com.

Main functions:
- Normal cell division
- Proper growth and optimal functioning of the bone marrow
- Normal blood formation
- Normal homocysteine
- Normal maternal tissue growth during pregnancy
- Normal metabolism of the immune system

Vitamin B9 is known by many as folate and plays an essential role in making and repairing DNA and producing red blood cells. Folate-rich foods include leafy, green vegetables, eggs, beans and lentils, shellfish and fruits. As the vitamin is extremely important during early pregnancy (in the prevention of neural tube defects), it is recommended that expectant mothers or women who are hoping to conceive take folate supplements during this period.
Functions
Tetrahydrofolate, which is the active form of folate in the body, acts as a co-enzyme in numerous essential metabolic reactions, with folate co-enzymes acting as acceptors and donors of one-carbon units. Folate co-enzymes play an important role in the metabolism of several amino acids, the constituents of proteins. The synthesis of the amino acid methionine from homocysteine, for example, requires a folate co-enzyme in addition to vitamin B12. Folate is also involved in the synthesis of nucleic acids (DNA and RNA) – the molecules that carry genetic information in cells – and in the formation of blood cells. Folates are therefore essential for normal cell division and proper growth, as well as for normal fetal development. In addition, folates are required for the prevention of anemia.

Dietary sources
Folates are found in a wide variety of foods, but in relatively low densities. Its richest sources are liver, dark green leafy vegetables, beans, wheat germ and yeast. Other natural sources are egg yolks, milk and dairy products, beets, orange juice and whole wheat bread. Fortified foods, such as breakfast cereals are among the best dietary sources of folate because they provide the vitamin as folic acid, a highly bioavailable vitamin form. Folates synthesized by intestinal bacteria do not contribute to homocysteine, whereas absorption occurs mainly in the upper part of the small intestine (jejunum).

Absorption and body stores
Most natural dietary folates exist as polyglutamates, which must be converted to the mono-glutamate form in the gut before absorption. The mono-glutamate form is absorbed in the proximal small intestine by an active carrier-mediated transport mechanism, and also by passive diffusion. Ingested folic acid is enzymatically reduced and methylated in the mucosa cells. The predominant form of folate in the plasma is 5-methyltetrahydrofolate (5-MTHF). Folates are widely distributed in the body’s tissues, primarily as polyglutamate derivatives. The main storage organ is the liver, which contains about half of the overall stores.

Bioavailability
Absorption of folic acid reaches almost 100% when it is consumed under fasting conditions. When folic acid is consumed with a portion of food, bioavailability is estimated to be 85% compared with free folic acid. The bioavailability of food folates is variable and incomplete. In fact, it has been estimated to be less than half that of folic acid.

Measurement
Different methods are used for the measurement of folates in foods and human tissue, including blood levels. Folates can be measured by microbiological assay using Lactobacillus casei as a test organism; this approach is considered to be the gold standard method for folate measurement but tends to be used in research rather than in clinical settings. Radio assays, based on competitive protein binding, are simpler to perform and are not affected by antibiotics, which give false low values in microbiological assays. High-performance liquid chromatography (HPLC) methods have also been established for the analysis of folates in human tissue and in foods. Folate status is assessed by measuring serum and red blood cell folate levels of methyltetrahydrofolate, which is the predominant folate. Serum folate level is considered a sensitive indicator of recent folate intake, with serum concentrations <7 nmol/L (1.5 ng/ml) likely to indicate a negative folate balance. Levels in the red blood cells are a better indicator of long-term status and to be representative of tissue folate stores. Levels <305 nmol/L (140 ng/ml) indicate inadequate folate status. Increased homocysteine levels may also indicate folate deficiency. Methyltetrahydrofolate is necessary for the conversion of homocysteine to methionine. Therefore, plasma homocysteine concentration increases when folate is not available in sufficient quantities. Although plasma homocysteine concentration is a sensitive indicator, it is not highly specific because it may be influenced by other nutrient deficiencies (such as vitamins B12 or B6), genetic abnormalities and renal insufficiency.

Stability
Most naturally-occurring forms of folate in food are unstable. For instance, fresh leafy vegetables stored at room temperature may lose up to 70% of their folate activity within three days. Up to 95% of folate can also be lost during cooking through leaching and also exposure to heat. Folic acid, which is commonly found in supplements and fortified foods, is more stable than natural folates.

Physiological interactions
- Efficient folate utilization depends on an adequate supply of other vitamins in the B-vitamin group, such as vitamins B12 and B6, as they are involved in the chemical reactions needed for folate metabolism. Vitamin C may also provide the conditions needed to preserve folates in the diet. However, a diet deficient in folates is also likely to be deficient in vitamin C.
- Several chemotherapeutic agents (e.g. methotrexate, trimethoprim, trimethoprim-sulfamethoxazole) inhibit the enzyme dihydrofolate reductase, which is necessary for the metabolism of folates. When nonsteroidal anti-inflammatory drugs (e.g. aspirin, ibuprofen) are taken in very large therapeutic doses, for example in the treatment of severe arthritis, folate metabolism may be disrupted.
- Many drugs may also interfere with the absorption, utilization and storage of folates. These include alcohol, cholestyramine and colchicine, which are used to lower blood cholesterol and antiepileptic agents such as phenytoin, as well as diphenylhydantoin and sulfasalazine, which are used in the treatment of ulcerative colitis. Drugs that reduce acidity in the intestine, such as antacids and modern anti-ulcer drugs, have also been reported to interfere with the absorption of folic acid. Early studies of oral contraceptives containing high levels of estrogen suggested an adverse effect on folate status, but this has not been supported by more recent studies on low dose oral contraceptives.

Deficiency
Folate deficiency can result from inadequate intake, defective absorption, abnormal metabolism or an increased requirement for the vitamin. Diagnosis of a subclinical deficiency relies on the demonstration of reduced red cell folate concentration, or other biochemical evidence such as increased homocysteine concentration. Early symptoms of folate deficiency are non-specific and may include tiredness, irritability and loss of appetite. Severe folate deficiency leads to megaloblastic anemia, a condition in which the bone marrow produces giant, immature red blood cells. At an advanced stage of anemia, symptoms of weakness, fatigue, shortness of breath, irritability, headaches and palpitations appear. Gastrointestinal problems may also result from severe folate deficiency, whereas deficiency during pregnancy can result in premature birth, low birth weight or reduced fetal development. In children, growth may be stunted and puberty could be delayed.

Folate deficiency is very common in many parts of the world and is therefore considered a global nutritional challenge. Reduced folate intake is often seen in people on special diets (e.g. weight-reducing diets) or disorders of the stomach (e.g. atrophic gastritis) and small intestine (e.g. celiac disease, sprue, Crohn’s disease), where folate deficiency may be the result of malabsorption. In conditions with a high rate of cell turnover (e.g. cancer, certain anemias and skin disorders), folate requirements are increased. This is also the case during both pregnancy and breastfeeding. People undergoing drug treatment, e.g. for epilepsy, cancer or an infection, are at high risk of developing a folate deficiency, as are patients with renal failure who require regular hemodialysis. Acute folate deficiencies have been reported to occur within a relatively short time in patients undergoing intensive care, especially those on total parenteral nutrition.
Reducing disease risk: therapeutic use

In situations where there is a risk of folate deficiency, daily oral folic acid supplementation is recommended, usually in a multivitamin preparation containing 400 μg of folic acid. It has been demonstrated that peri-conceptional (before and during the first 28 days after conception) supplementation of women with folic acid can decrease the risk of neural tube defects by 72 - 100%. Therefore, a daily intake of 600 μg folic acid, in addition to a healthy diet eight weeks prior to and during the first 12 weeks of pregnancy is recommended globally to women of reproductive age.

There is evidence that adequate folate status may also reduce the risk of the incidence of other birth defects, including cleft lip and palate, certain heart defects and limb malformations. Results from intervention studies have shown that a multivitamin supplement containing folic acid is more effective in decreasing the risk of neural tube defects and other birth defects than folic acid alone.

Recommended Daily Intake (RDI)

To set the new dietary recommendation for vitamin B9, the Dietary Folate Equivalent (DFE) has been used, reflecting the higher bioavailability of synthetic folic acid in supplements compared to that of naturally occurring food folates. 1 μg of food folate provides 1 μg of DFE for example. 1 μg of folic acid (supplement) taken on an empty stomach provides 2 μg DFE. It is recommended that adults take 1 μg of folic acid taken with meals or as fortified food provides 3 μg DFE. 1 μg of folic acid taken on an empty stomach provides 2 μg DFE. It is recommended that adults consume 400 μg daily, whereas pregnant women need 600 μg.

Safety

Oral folic acid is not considered to be toxic to humans. However, it has been claimed that high doses of folic acid may counteract the effect of antiepileptic medication and so increase the frequency of seizures in susceptible patients. Folic acid at very high doses can also potentially mask vitamin B12 deficiency and thereby delay its diagnosis. It should therefore not be used indiscriminately in patients with anemia because of the risk of damage to the nervous system due to vitamin B12 deficiency. The US Food and Nutrition Board (FNB) (1998) set the UL of folic acid from fortified foods or supplements at 1 mg/day for adults.

Supplements and food fortification

Folic acid is available as oral preparations alone or in combination with other vitamins or minerals (e.g. iron), or as an aqueous solution for injection. As the acid is poorly soluble in water, folate salts are used to prepare liquid dosage forms. Folinic acid (also known as leucovorin or citrovorum factor) is a derivative of folic acid administered by intramuscular injection to circumvent the action of dihydrofolate reductase inhibitors, such as methotrexate. It is not otherwise indicated for the prevention or treatment of folic acid deficiency. Folic acid is added to a variety of foods, the most important of which are flour, breakfast cereals, certain beverages, salt and baby foods. To reduce the risk of neural tube defects, cereal grains are fortified with folic acid in some countries. In the US and Canada, for example, all enriched cereal grains (e.g. enriched bread, pasta, flour, breakfast cereals, and rice) are required to be fortified with folic acid.

Production

Folic acid is manufactured on a large scale by chemical synthesis, using a variety of processes.

Recommended daily intakes (RDI) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>&lt;6 months</td>
<td>65 μg (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7 – 12 months</td>
<td>80 μg (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1 – 3 years</td>
<td>150 μg</td>
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<tr>
<td>Children</td>
<td>4 – 8 years</td>
<td>200 μg</td>
</tr>
<tr>
<td>Children</td>
<td>9 – 13 years</td>
<td>300 μg</td>
</tr>
<tr>
<td>Adults</td>
<td>≥14 years</td>
<td>400 μg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>14 – 50 years</td>
<td>600 μg</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>14 – 50 years</td>
<td>600 μg</td>
</tr>
</tbody>
</table>

* Adequate Intake (AI)

History

1931 Wills observes the effect of liver and yeast extracts on treating tropical macrocytic anemia and concludes that this disorder must be due to a dietary deficiency. She recognizes that yeast contains a curative agent equal in potency to that of liver.

1939 Hogan and Parrott identify an antianemia factor in chicks in liver extracts, which they name Vitamin BC.

1940 Mitchell and colleagues suggest the name ‘folic acid’ (folium is Latin for leaf) for the factor responsible for growth stimulation of Streptococcus lactis, which they isolate from spinach and suspect of having vitamin-like properties for animals.

1941 Discovery of growth factors for Lactobacillus casei and Streptococcus lactis. Snell and Peterson coin the term ‘riboflavin’.

1945 Angier and team report the synthesis of a compound identical to the L. casei factor isolated from liver. They later describe the chemical structures of the basic and related compounds.

1951 Spies demonstrates that folic acid cures megaloblastic anemia during pregnancy.

1962 Butcher observes the effect of liver and yeast extracts in treating tropical macrocytic anemia and concludes that this disorder must be due to a dietary deficiency. She recognizes that yeast contains a curative agent equal in potency to that of liver.

1992 The US Public Health Service recommends that all women of childbearing age consume 0.4 mg (400 μg) of folate daily in order to reduce the risk of fetal malformations such as spina bifida and other neural tube defects.

1993 Butterworth finds that higher than normal serum levels of folic acid are associated with decreased risk of cervical cancer in women infected with human papillomavirus. Also, Cavan describes that first-time occurrence of neural tube defects may be largely eliminated with a multivitamin containing folic acid taken in the periconceptional period.

1998 Fortification of all enriched cereal grains (e.g. enriched bread, pasta, flour, rice and breakfast cereals) with folic acid becomes mandatory in the US and in Canada. In Hungary, wheat flour is fortified with folic acid.

2000 Mandatory fortification of wheat flour with folic acid is established in Chile.

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Vitamin B12 (Cyanocobalamin)

Vitamin B12, which is only found in foods of animal origin, is the largest and most complex of all the vitamins. In the body, the vitamin supports the development of red blood cells and DNA, maintains healthy nerve cells and releases energy from food. Mild deficiencies of B12 are not uncommon in elderly people, usually due to poor diet or because individuals have less stomach acid which is needed to absorb the vitamin.

Synonyms:
Cobalamin, Coenzyme B12, Adenosylcobalamin, AdoCbl, cobamamide, Antipernicious-anemia factor, Castle’s extrinsic factor, animal protein factor.

Chemistry:
The structure of vitamin B12 is based on a corrin ring, which has two of the pyrrole rings directly bonded. The central metal ion is Co (cobalt). Four of the six coordinations are provided by the corrin ring nitrogens, and a fifth by a dimethylbenzimidazole group. The sixth coordination partner varies, being a cyano group (-CN) (cyanocobalamin), a hydroxyl group (-OH) (hydroxycobalamin), a methyl group (-CH3) (methylcobalamin) or a 5’-deoxyadenosyl group (5'-deoxyadenosylcobalamin).

Food:

<table>
<thead>
<tr>
<th></th>
<th>µg/100g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef liver</td>
<td>65</td>
</tr>
<tr>
<td>Crab</td>
<td>27</td>
</tr>
<tr>
<td>Blue mussel</td>
<td>8</td>
</tr>
<tr>
<td>Steak</td>
<td>5</td>
</tr>
<tr>
<td>Codfish</td>
<td>3.5</td>
</tr>
<tr>
<td>Cheese (Camembert)</td>
<td>3</td>
</tr>
<tr>
<td>Eggs</td>
<td>1 - 3</td>
</tr>
</tbody>
</table>

For scientific sources, please contact info.nutritionscience@dsm.com.

Main functions:
- Coenzyme-function in intermediary metabolism, especially in cells of the nervous tissue, bone marrow and gastrointestinal tract
- Essential growth factor
- Formation of blood cells and myelin sheaths
- Regeneration of folate
- Involved in the production of melatonin (controls the release of many hormones in the body and is involved with the sleep/wake cycle)
hydroxy-, methyl- and 5’-deoxy- adenosyl-cobalamins are the products are the main source of vitamin B12 in the human diet. Vitamin B12 is produced exclusively by microbial synthesis in

**Dietary sources**

Vitamin B12 is produced exclusively by microbial synthesis in the digestive tract of animals. Therefore, animal protein products are the main source of vitamin B12 in the human diet. Other sources include fish, eggs and dairy products. In foods, hydroxy-, methyl- and 5’-deoxy- adenosyl-cobalamins are the main cobalamins present. Bacteria in the intestine synthesize vitamin B12, but not in areas where absorption occurs. Some foods are also fortified with vitamin B12.

**Absorption and body stores**

Vitamin B12 from food sources is bound to proteins and only released by an adequate concentration of hydrochloric acid in the stomach. Free vitamin B12 is then immediately bound to glycoproteins originating from the stomach and salivary glands. This glycoprotein complex protects vitamin B12 from chemical denaturation. Gastrointestinal absorption of vitamin B12 occurs in the small intestine by an active process requiring the presence of an intrinsic factor, another glycoprotein, which the gastric parietal cells secrete after being stimulated by food. The absorption of physiological doses of vitamin B12 is limited to approximately 2ug/dose. The vitamin B12 intrinsic factor complex is then absorbed through phagocytosis by specific ileal receptors. Once absorbed, the vitamin is transferred to a plasma-transport protein which delivers the vitamin to target cells. A lack of intrinsic factor prevents vitamin B12 absorption. If this is untreated, potentially irreversible neurological damage and life-threatening anemia develops (see Deficiency).

Regardless of dose, approximately 1% of vitamin B12 is absorbed by passive diffusion, so this process becomes quantitatively important at pharmacological levels of exposure. Once absorbed, vitamin B12 is stored principally (60%) in the liver. The average B12 content is approximately 2µg/dose. The vitamin B12 intrinsic factor complex is then absorbed through phagocytosis by specific ileal receptors. Once absorbed, the vitamin is transferred to a plasma-transport protein which delivers the vitamin to target cells. A lack of intrinsic factor prevents vitamin B12 absorption. If this is untreated, potentially irreversible neurological damage and life-threatening anemia develops (see Deficiency).

Measurement

Measurement of vitamin B12 in plasma is routinely used to determine deficiency but may not be a reliable indication in all cases. In pregnancy, for example, tissue levels are normal, but serum levels are low. Vitamin B12 can be measured by chemical, microbiological or immunoassay isotope dilution methods. Microbiological assays, which are widely used for blood and tissue samples, are sensitive but non-specific. Serum cobalamin concentration is often determined by automated immunoassays using intrinsic factor as a binding agent. These assays have mainly replaced microbiological methods.

Data in literature about vitamin B12 serum concentration varies. However, values under 150 – 150 pmol/L are considered to reflect deficiency, whereas values over 150 – 200 pmol/L represent an adequate status. Major vitamin B12-dependent metabolic processes include the formation of methionine from homocysteine, and the formation of succinyl coenzyme A from methylenylcoenzyme A. Thus, apart from directly determining vitamin B12 concentration in the blood, elevated concentrations of both methylenalonic acid (MMA) and homocysteine may indicate a vitamin B12 deficiency. Vitamin B12 concentrations can also be measured using the novel biomarker holotC.

Stability

Vitamin B12 is stable to heat, but slowly loses its activity when exposed to light, oxygen and acid or alkali-containing environments. Loss of activity during cooking is due to the water solubility of vitamin B12 rather than its destruction.

**Physiological interactions**

- Absorption of cobalamins is impaired by alcohol and vitamin B6 deficiency. Furthermore, a number of drugs reduce the absorption of vitamin B12, and supplementation with the affected nutrient may be necessary:
  - Antibiotics (e.g. chloramphenicol)
  - Anti-diabetics (e.g. metformin and phenformin)
  - Anti-epileptic drugs
  - Anti-goat medication (Colchicine)
  - Stomach medication (H2 receptor antagonists, Proton pump inhibitors)
  - Nitrous oxide (anesthetic)
  - Oral contraceptives
  - Tuberculostatics (Para-aminosalicylic acid)
  - Several anticonvulsants – phenobarbitone, primidone, phenytoin and ethylphenacemide – can alter the metabolism of cobalamins in the cerebrospinal fluid and lead to neuropsychic disturbances. Several substituted amide, lactone and lactam analogues of cyanocobalamin compete with binding sites on intrinsic factor and lead to depressed absorption of the vitamin. Nitrous oxide (anesthetic) also interferes with cobalamin metabolism.

**Recommended daily intakes (RDI)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Life stage</th>
<th>Dose/day**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants</strong></td>
<td>&lt;6 months</td>
<td>0.4 µg (AI)</td>
</tr>
<tr>
<td></td>
<td>7 – 12 months</td>
<td>0.5 µg (AI)</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>1 – 3 years</td>
<td>0.9 µg</td>
</tr>
<tr>
<td></td>
<td>4 – 8 years</td>
<td>1.2 µg</td>
</tr>
<tr>
<td></td>
<td>9 – 13 years</td>
<td>1.8 µg</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>&gt;14 years</td>
<td>2.4 µg</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>14 – 50 years</td>
<td>2.6 µg</td>
</tr>
<tr>
<td><strong>Breastfeeding</strong></td>
<td>14 – 50 years</td>
<td>2.8 µg</td>
</tr>
</tbody>
</table>

*Institute of Medicine (2001)

**Adapted from RDI**


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RDIs: Allowable levels of nutrients vary depending on national regulations and the final application.
Deficiency
Vitamin B12 deficiency affects 10 – 15% of individuals over the age of 60. Deficiency of vitamin B12 leads to defective DNA synthesis in cells, which affects the growth and repair of all cells. The tissues most affected are those with the greatest rate of cell turnover, e.g. those of the hematopoietic system. This can lead to megaloblastic anemia (characterized by large and immature red blood cells) and neuropathy, with numerous symptoms including: glossitis, weakness, loss of appetite, loss of taste and smell, impotence, irritability, memory impairment, mild depression, hallucination, breathlessness (dyspnea) on exertion, tingling and numbness (paraesthesia). Vitamin B12 deficiency can also lead to hyperhomocysteinemia, a possible risk factor for atherogenic vascular disease. Low vitamin B12 has been associated with a variety of chronic diseases of aging such as dementia and cognitive impairment, cardiovascular disease (CVD) and osteoporosis.

The symptoms of vitamin B12 deficiency are similar to those of folic acid deficiency, the major difference being only that vitamin B12 deficiency is associated with spinal cord degeneration. If folic acid is used to treat vitamin B12 deficiency, anemia may be alleviated but the risk of damage to the nervous system remains. Nervous dysfunction due to the lack of vitamin B12 can be irreversible and potentially life threatening if left untreated. It is therefore essential to diagnose the deficiency accurately before starting therapy.

Deficiency is usually caused as a result of vitamin B12 malabsorption. Without intrinsic factor, absorption is not possible and a severe and persistent deficiency develops that cannot be prevented by the usual dietary intakes of vitamin B12.

Groups at risk
- Vegetarians
- The elderly
- Alcoholics
- People with:
  - pernicious anemia (autoimmune disease, chiefly affects people post middle age)
  - food-bound vitamin B12 malabsorption (in patients receiving long-term treatment with certain drugs, elderly patients with gastric atrophy, patients with atrophic gastritis)
  - after gastrectomy
  - after ingestion of corrosive agents with destruction of gastric mucosa
- lesions of the small bowel; bacterial overgrowth; patients with small intestinal defects; inborn errors of cobalamin metabolism etc.
- pancreatic insufficiency
- AIDS

Reducing disease risk: therapeutic use

Pernicious anemia
Pernicious anemia patients are traditionally treated with intramuscular injections of vitamin B12; large oral doses of the vitamin are also effective but require lifetime therapy. When used alone, oral doses of at least 100 µg/day are necessary, although single weekly oral doses of 1,000 µg have proved satisfactory in some cases.

Hyperhomocysteinemia
Homocysteine appears to be a nerve and vessel toxin, promoting mortality and CVD as well as stroke, Alzheimer’s disease, birth defects, recurrent pregnancy loss, and eye disorders. Keeping homocysteine at levels associated with lower rates of disease requires adequate vitamin B12, folic acid and vitamin B6 intake.

Cancer
Vitamin B12 deficiency may lead to an elevated rate of DNA damage and altered methylation of DNA. These are obvious risk factors for cancer. In a recent study, chromosome breakage was minimized in young adults by supplementation with 700 µg of folic acid and 7 µg of vitamin B12 daily in cereals for two months.

Recommended Daily Intake (RDI)
The US Institute of Medicine (IOM) recommends that anyone over 50 years should consume most of their vitamin B12 from fortified foods or supplements. During pregnancy, it is recommended that women consume 2.6 µg/day and up to 2.8 µg/day during breastfeeding to cover the additional requirements of the fetus/infant. The Committee on Nutrition of the American Academy of Pediatrics recommends a daily vitamin B12 intake of 0.5 µg/100 kcal energy intake for infants and preadolescent children. Other authorities have suggested intakes of 0.4 – 0.5 µg (0 – 1 year of age), 0.9 – 1.8 µg (1 – 10 years of age) and 2.4 µg (>10 years). The ‘average’ Western diet probably supplies 1 – 10 µg/day, but this can range from 1 – 100 µg/day.

Safety
Large intakes of vitamin B12 from food or supplements have caused no toxicity in healthy people. No adverse effects have been reported from single oral doses as high as 100 mg and chronic administration of 1 mg (500 times the RDI) weekly for up to 5 years. Moreover, there have been no reports of carcinogenic or mutagenic properties, and studies to date indicate no teratogenic potential. The main food safety authorities have not set a UL for vitamin B12 because of its low toxicity.

Supplements and food fortification
The principal form of vitamin B12 used in supplements is cyanocobalamin. It is available in the form of injections and as a nasal gel for the treatment of pernicious anemia. Cyanocobalamin is also available in tablet and oral liquid form for vitamin B-complex, multivitamin and vitamin B12 supplements. Vitamin B12 is widely used to enrich cereals and certain beverages. Fortification with vitamin B12 is especially important for products aimed at people with a low dietary vitamin B12 intake, such as vegans.

Production
Vitamin B12 is produced commercially from bacterial fermentation, usually as cyanocobalamin.

History
The first case of pernicious anemia and its possible relation to disorders of the digestive system is described by Combe.

Combe and Addison identify clinical symptoms of pernicious anemia.

Whipple and Robeck-Hobbs discover the benefits of consuming liver in regenerating blood in anemic dogs.

Minot and Murphy report that a diet rich in large quantities of raw liver restores the normal level of red blood cells in patients with pernicious anemia. Liver concentrates are developed and studies on the presumed active principle(s) (antipernicious anemia factor) are initiated.

Rickes, Smith and Parker, working separately, isolate a crystalline red pigment which they name vitamin B12.

West shows that injections of vitamin B12 dramatically benefit patients with pernicious anemia.

Pierce and team isolate two crystalline forms of vitamin B12 that are equally effective in combating pernicious anemia. One form is found to contain cyanide (cyanocobalamin), while the other is not (hydroxocobalamin).

Eschenmoser and colleagues in Switzerland and Woodward and team in the US synthesize vitamin B12 from cultures of certain bacteria/fungi.

Total chemical synthesis of vitamin B12 by Woodward.
### Glossary

**Acceptable Macronutrient Distribution Range (AMDR)**

AMDR is the percentage range of protein, fat and carbohydrate intakes that is associated with a reduced risk of chronic disease, while also providing adequate intakes of essential nutrients.

**Adequate Intake (AI)**

Only established when an EAR (and thus an RDI) cannot be determined because the data are not clear-cut enough; a nutrient has either an RDI or an AI. The AI is a value based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group (or groups) of healthy people. The AIs for children and adults are expected to meet or exceed the amount needed to maintain a defined nutritional state or criterion of adequacy in essentially all members of a specific apparently healthy population.

**Antioxidant**

Antioxidant substances, such as vitamins and carotenoids, are thought to protect the body against the destructive effects of free radicals. Antioxidants neutralize free radicals by donating one of their own electrons, ending the electron-"stealing" reaction. They act as scavengers, helping to prevent cell and tissue damage that could lead to CVD and cancer.

Oxidation of low-density lipoprotein (LDL) cholesterol is important in the development of fatty build-ups in the arteries (atherosclerosis). Antioxidant substances, such as vitamins and carotenoids, can potentially prevent LDL oxidation and its harmful effects.

**Carotenoids**

Any class of mainly yellow, orange, or red fat-soluble pigments produced by plants and algae, as well as several bacteria and fungi. Dietary carotenoids act as a type of antioxidant for humans and provide overall health benefits, including decreased risk of disease and enhanced immunity.

**Dietary Reference Intake (DRI)**

DRI is an umbrella term for a set of nutrient reference values that includes the estimated average requirements (EAR), the recommended daily intake (RDI), the adequate intake (AI) and the acceptable macronutrient distribution range (AMDR). These values guide professionals on the amount of a nutrient needed to maintain health in an otherwise healthy individual or group of people. DRIs also include the tolerable upper intake level (UL), which is the maximum amount of a nutrient that can be consumed safely over a long period of time.

**Estimated Average Requirement (EAR)**

The amount of a nutrient that is estimated to meet the requirement of half of all healthy individuals in a given age and gender group. This value is based on a thorough review of the scientific literature.

**International Unit (IU)**

A unit of measurement for the amount of a substance (e.g. vitamin), based on measured biological activity or effect.

**Mediterranean diet**

A dietary style based on food patterns typical of Mediterranean countries: plant foods, fruit, olive oil, dairy products (primarily cheese and yogurt), fish and poultry consumed in low to moderate amounts and red meat consumed in low amounts. Overall, the Mediterranean diet consists of a healthier balance between (higher) omega-3 and (lower) omega-6 fatty acids (compared to the Western diet). Research has shown that people who follow this diet are less likely to develop CVD.

**Osteomalacia**

A disease occurring among adults that is characterized by softening of the bones due to loss of bone mineral. Osteomalacia is characteristic of vitamin D deficiency in adults, while children with vitamin D deficiency suffer from soft and deformed bones (rickets). Many of the effects of the disease overlap with the more common osteoporosis, but the two diseases are significantly different. Osteomalacia is specifically a defect in mineralization of the protein (collagen) framework.

**Pellagra**

A disease caused by having too little vitamin B3 (niacin) or the amino acid tryptophan in the diet. It can also occur if the body fails to absorb these nutrients, after gastrointestinal diseases or with alcoholism. Symptoms of pellagra include diarrhea, mental confusion, and scaly skin sores.

**Population Reference Intake (PRI)**

The PRI, in most countries called RDI, defines an adequate nutrient intake level that most, if not all, individuals of a population or a specific population group should obtain to satisfy their requirements. PRIs were set by the European Scientific Committee on Food (SCF).

**Randomized Controlled Trial (RCT)**

A clinical trial with at least one active treatment group (e.g. taking a vitamin) and a control (e.g. placebo) group. In blind RCTs, participants are chosen for the experimental and control groups (e.g. placebo-controlled) at random and are not told whether they are receiving the active or placebo treatment until the end of the study. An RCT in which neither the investigators administering the treatment, nor the participants know which participants, are receiving the experimental treatment and which are receiving the placebo is called ‘double blind’. RCTs are always prospective studies i.e. a study that follows participants for a period of time and is observing an outcome, such as the development of a disease. RCTs, the gold standard for intervention studies, are considered to be of high quality because the risk of bias is minimized when the trial is blinded. An RCT can provide evidence and can establish cause-and-effect relationships (hypothesis testing).
Rickets

A softening of bones in children potentially leading to fractures and deformity. Rickets is among the most common childhood diseases in many developing countries. The predominant cause is a vitamin D deficiency, but lack of adequate calcium may also lead to rickets.

RDI refers to the average daily dietary intake of a nutrient that is sufficient to meet the nutritional requirements of 97 – 98% of a population.

A disorder caused by lack of vitamin C. Symptoms include anemia, bleeding gums, tooth loss, joint pain, and fatigue. Scurvy is treated by supplying foods high in vitamin C and vitamin C supplements.

A daily average intake from food and beverages for certain nutrients that may help in the prevention of chronic disease. SDT (intake per day on average) for vitamin C is 220 mg in men and 190 mg in women. This is equivalent to the 90th centile of intake in the Australian and New Zealand populations, to be attained by replacing nutrient-poor, energy-dense foods and drinks with plenty of vegetables, legumes and fruit.

Tolerable UL is the highest continuing daily intake of a nutrient that is likely to pose no risks of adverse health effects for almost all individuals. However, as intake increases above the UL, the risk of adverse effects increases.

A dietary habit chosen by many people in developed countries, and increasingly in developing countries. High intakes of red meat, sugar, fat, salt, and refined grains characterize it. Research has shown that people who eat lots of foods in the Western category have a 35% higher heart attack risk than those who ate less meat, eggs, and fried and salty foods (see Mediterranean diet). In addition, chronic illnesses and health problems such as obesity, atherosclerosis, high blood pressure, high cholesterol, and cancer are thought to be either wholly or partially related to a Western diet.

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Western diet

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