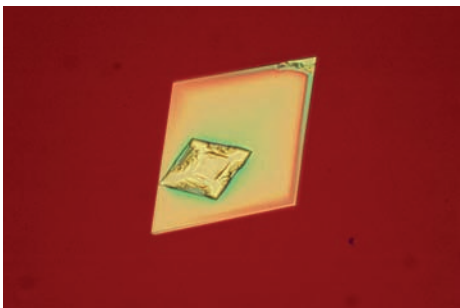
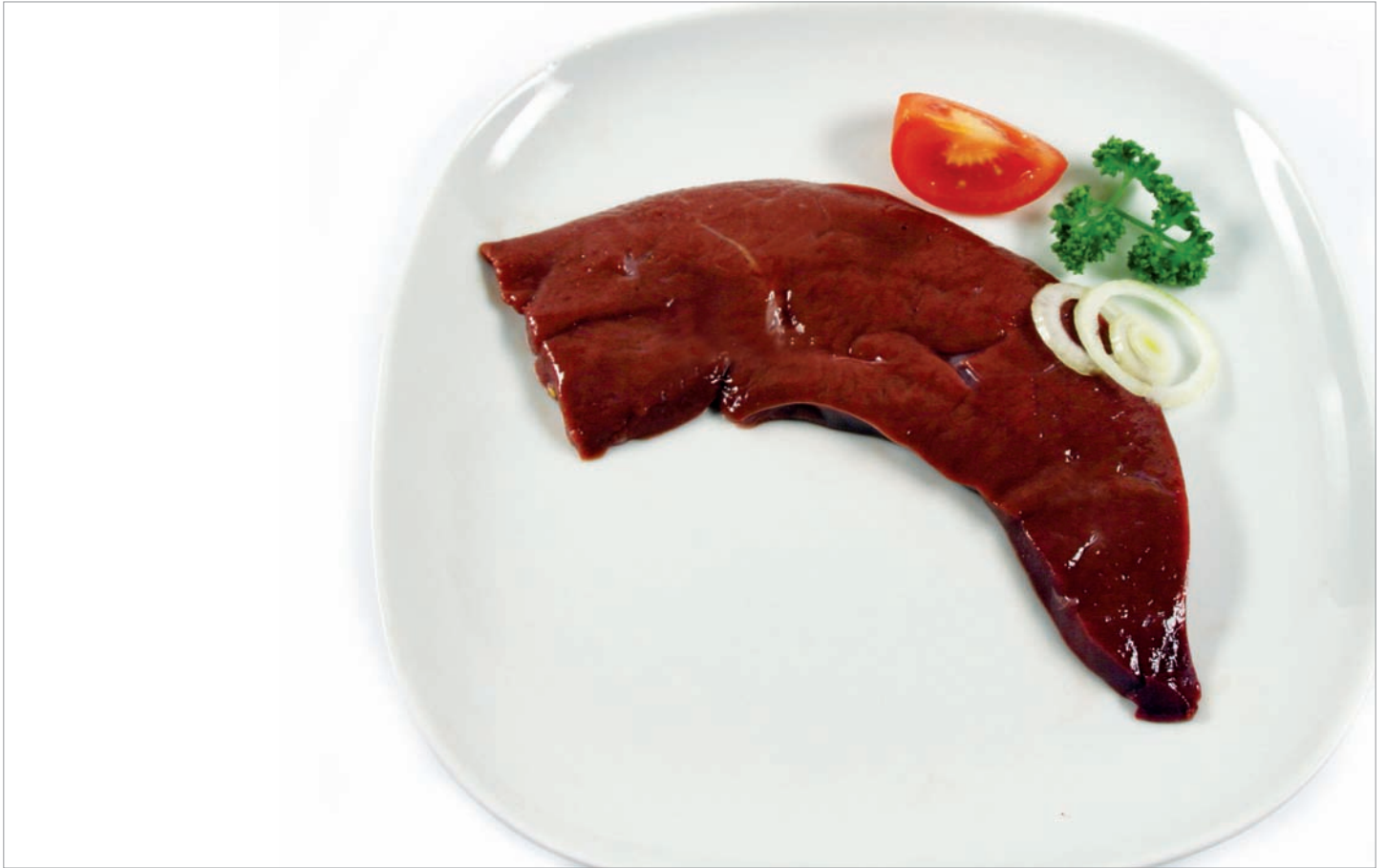


Vitamin A



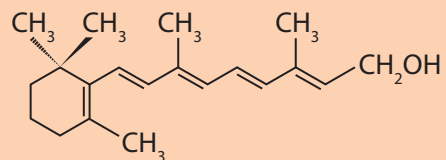
Vitamin A crystals in polarised light

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).



Molecular formula of vitamin A (retinol)

Introduction

Vitamin A is a generic term for a group of lipid soluble compounds related to retinol. Retinol is often referred to as preformed vitamin A. It is found only in animal sources, mainly as retinyl esters and in food supplements. Many cultures have used ox liver as an excellent source of vitamin A to cure night blindness. The liver was first pressed to the eye and then eaten; the Egyptians described this cure at least 3,500 years ago. Beta-carotene and other carotenoids that can be converted to vitamin A by an enzymatic process in the body are referred to as provitamin A. They are found only in plant sources.

Functions

Retinal, the oxidised metabolite of retinol, is required for the process of vision. Retinoic acid, another vitamin A metabolite, is considered to be responsible for all non-visual functions of vitamin A. Retinoic acid combines with specific nuclear receptor proteins which bind to DNA and regulate the expression of various genes, thereby influencing numerous physiological processes. Retinoic acid is therefore classified as a hormone.

Vision

Receptor cells in the retina of the eye (rod cells) contain a light-sensitive pigment called rhodopsin, which is a complex of the protein opsin and the vitamin A metabolite retinal. The light-induced disintegration of the pigment triggers a cascade of events which generate an electrical signal to the optic nerve. Rhodopsin can only be regenerated from opsin and vitamin A. Rod cells with this pigment can detect very small amounts of light, making them important for night vision.

Cellular differentiation

The many different types of cells in the body perform highly specialised 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. Vitamin A is necessary for normal differentiation of epithelial cells, the cells of all tissues lining the body, such as skin, mucous membranes, blood vessel walls and the cornea. In vitamin A deficiency, cells 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 required for the normal functioning of the immune system and therefore helps to protect against infections in a number of ways. It is essential in maintaining

Vitamin A content of foods

Food	Vitamin A (Retinol) µg/100g	RE µg/100g
Veal liver	28000	28000
Carrots	-	1500
Spinach	-	795
Melon (cantaloupe)	-	784
Butter	590	653
Cheese (Cheddar)	390	440
Egg	276	272
Broccoli	-	146
Salmon	41	41
Milk (whole)	35	35

the integrity and function of the skin and mucosal cells, which function as a mechanical barrier 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 defence of the body against pathogens.

Main functions in a nutshell:

- Vision
- Reproduction
- Growth and development
- Cellular differentiation
- Immune function

Dietary sources

The richest food source of preformed vitamin A is liver, with considerable amounts also found in egg yolk, whole milk, butter and cheese. Provitamin A carotenoids are 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 is still the measurement generally used on food and supplement labels. In order to standardise vitamin A measurement, it has now been internationally agreed to state vitamin A activity in terms of a new unit called the retinol equivalent, or RE, which accounts for the rate of conversion of carotenoids to retinol.

1 RE = 1 µg retinol
 = 6 µg beta-carotene
 = 12 µg other provitamin A carotenoids
 = 3.33 IU vitamin A activity from retinol

Absorption and body stores

Vitamin A is absorbed in the upper part of the small intestine. Provitamin A carotenoids can be cleaved into retinol via an enzymatic process. Preformed vitamin A occurs as retinyl esters of fatty acids. They are hydrolysed and retinol is absorbed into intestinal mucosal cells (i.e. enterocytes). After re-esterification it is incorporated into chylomicrons, excreted into lymphatic channels, delivered to the blood and transported to the liver. Vitamin A is stored in the liver as retinyl esters; stores are enough for one to two years in most adults living in industrialised countries.

Measurement

Vitamin A can be measured in the blood and other body tissues by various modern techniques. For rapid field tests, a method has been developed recently using dried blood spots. Typical serum level is 1.1-2.3 µmol/L. According to the WHO, plasma levels of $\leq 0,35$ µmol/L indicate a vitamin A deficiency.

Stability

Vitamin A is sensitive to oxidation by air. Loss of activity is accelerated by heat and exposure to light. Oxidation of fats and oils (e.g. butter, margarine, cooking oils) can destroy fat soluble vitamins including vitamin A. The presence of antioxidants such as vitamin E therefore contributes to the protection of vitamin A.

Interactions

Positive interactions

- Vitamin E protects vitamin A from being oxidised; hence, adequate vitamin E status protects vitamin A status.

Negative interactions

- Disease and infection, especially measles, compromise vitamin A status and conversely, poor vitamin A status decreases resistance to diseases.
- Chronic heavy alcohol intake can impair liver storage of vitamin A.
- Acute protein deficiency interferes with vitamin A metabolism; similarly, too little fat in the diet interferes with the absorption of both vitamin A and carotenoids.
- Vitamin A deficiency may result in impaired iron absorption and decrease its utilisation for erythropoiesis, thereby potentially exacerbating iron deficiency anaemia.
- Zinc deficiency may adversely affect mobilisation of vitamin A from hepatic stores and absorption of vitamin A from the gut.

Deficiency

Vitamin A deficiency is rare in the Western world, but in developing countries it is one of the most widespread, yet preventable, causes of blindness. The earliest symptom of vitamin A deficiency is impaired dark adaptation, or night blindness. Severe deficiency causes a condition called xerophthalmia, characterised by changes in the cells of the cornea that ultimately result in corneal ulcers, scarring and blindness. The appearance of skin lesions (follicular hyperkeratosis) is also an early indicator of inadequate vitamin A status. Growth retardation is a common sign in children. Because vitamin A is required for the normal functioning of the immune system, even children who are only mildly deficient in vitamin A have a higher incidence of respiratory disease and diarrhoea, as well as a higher rate of mortality from infectious diseases, than children who consume sufficient vitamin A. Some diseases may themselves induce vitamin A deficiency, most notably liver and gastrointestinal diseases, which interfere with the absorption and utilisation of vitamin A. Vitamin A deficiency during pregnancy leads to malformations during foetal development.



Child suffering from corneal scar

Disease prevention and therapeutic use

Studies have shown that vitamin A supplementation given to children aged over 6 months reduces all-cause mortality by between 23% and 30% in low income countries. The beneficial effect is assumed to be due to the prevention of vitamin A deficiency. The World Health Organisation (WHO) recommends that supplements should be given when children are vaccinated. The currently recommended doses are 100,000 IU at age 6-11 months and 200,000 IU at age ≥ 12 months every 3-6 months.

Xerophthalmia is treated with high doses of vitamin A (50,000-200,000 IU 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 lactating women are the main 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 programmes for the prevention of vitamin A deficiency, infants < 6 months of age receive a dose of 50,000 IU of vitamin A, and children between six months and one year receive 100,000 IU every 4-6 months, while 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 been found to increase the vitamin A content of breast milk. However, caution is necessary when considering vitamin A therapy for lactating women, otherwise a co-existing pregnancy may be endangered: during pregnancy, a daily dose of 10,000 IU vitamin A should not be exceeded.

Administration of high doses of vitamin A to children with measles complications, but no overt signs of vitamin A deficiency, decreases mortality by over 50% and significantly lowers morbidity.

Natural and synthetic vitamin A analogues have been used to treat psoriasis and severe acne.

Current recommendations in the USA

RDA*

Infants	≤ 6 months	400 μg (Adequate Intake, AI)
Infants	7-12 months	500 μg (AI)
Children	1-3 years	300 μg
Children	4-8 years	400 μg
Children	9-13 years	600 μg
Males	≥ 14 years	900 μg
Females	≥ 14 years	700 μg
Pregnancy	14-18 years	750 μg
Pregnancy	≥ 19 years	770 μg
Lactation	14-18 years	1,200 μg
Lactation	≥ 19 years	1,300 μg

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

Recommended Dietary Allowance (RDA)

The recommended daily intake of vitamin A varies according to age, sex, risk group and other criteria applied in individual countries (700–1000 µg RE/day for men, 600–800 µg RE/day for women). In the USA the RDA for adults is 900 µg (men) and 700 µg (women) per day of preformed vitamin A (retinol). During lactation, an additional 500–600 µg per day are recommended. Infants and children, due to their smaller body size, have a lower RDA than adults.

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, spill into the blood, and produce adverse effects (liver damage, bone abnormalities and joint pain, alopecia, headaches, vomiting, and skin desquamation). Hypervitaminosis A can occur acutely following very high doses 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.

Normal foetal development requires sufficient vitamin A intake, but consumption of excess retinol during pregnancy is known to cause malformations in the newborn.

Several recent prospective studies suggest that long-term intakes of preformed 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 beta-carotene, were associated with adverse effects on bone health. Current levels of vitamin A in fortified foods are based on RDA levels, ensuring that there is no realistic possibility of vitamin A overdosage in the general population. In the vast majority of cases, signs and symptoms of toxicity are reversible upon cessation of vitamin A intake. Beta-carotene is considered a safe form of vitamin A because it is converted by the body only as needed.

The Food and Nutrition Board of the Institute of Medicine (2001) and the EC Scientific Committee on Food (2002) have set the tolerable upper intake level (UL) 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 gelatine capsules, as chewable or effervescent tablets, or in ampoules. It is also included in most multivitamins. Retinyl acetate, retinyl palmitate and retinal are the forms of vitamin A most commonly used in supplements.

Margarine and milk are commonly fortified with vitamin A. Beta-carotene is added to margarine and many other foods (e.g. fruit drinks, salad dressings, cake mixes, ice cream) both for its vitamin A activity and as a natural food colourant.

Industrial 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.



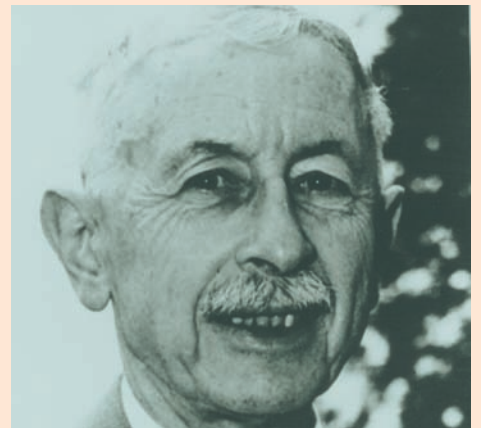
History

Although it has been known since ancient Egyptian times that certain foods, such as liver, would cure night blindness, vitamin A per se was not identified until 1913. Its chemical structure was defined by Paul Karrer in 1931. Professor Karrer received a Nobel Prize for his work because this was the first time that a vitamin's structure had been determined.

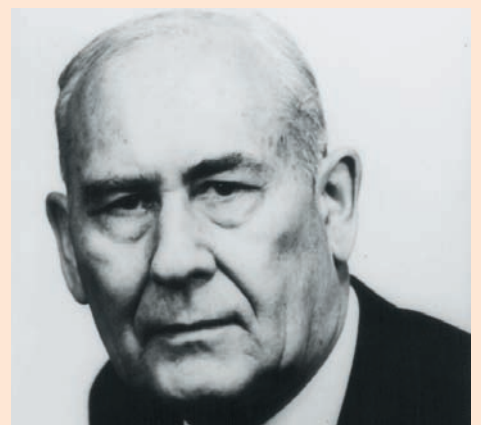
- 1831** Wackenroder isolates the orange-yellow colourant from carrots and names it "carotene."
- 1876** Snell successfully demonstrates that night blindness and xerophthalmia can be cured by giving the patient cod liver oil.
- 1880** Lunin discovers that, besides needing carbohydrates, fats and proteins, experimental animals can only survive if given small quantities of milk powder.
- 1887** Arnaud describes the widespread presence of carotenes in plants.
- 1909** Stepp successfully extracts the vital liposoluble substance from milk.
- 1915** McCollum differentiates between "fat-soluble A" and "water-soluble B."
- 1929** The vitamin A activity of beta-carotene is demonstrated in animal experiments.
- 1931** Karrer isolates practically pure retinol from the liver oil of a species of mackerel. Karrer and Kuhn isolate active carotenoids.
- 1946** Isler undertakes the first large-scale industrial synthesis of vitamin A.
- 1984** Sommer demonstrates that vitamin A deficiency is a major cause of infant mortality in Indonesia.
- 1987** Chombon in Strasbourg and Evans in San Diego, and their respective coworkers, simultaneously discover the retinoic acid receptors in cell nuclei.
- 1997** UNICEF, the World Health Organisation (WHO), and the governments of countries including Canada, the United States and the United Kingdom, as well as national governments in countries where vitamin deficiency is widespread, launch a global campaign to distribute high-dose vitamin A capsules to malnourished children.



Elmer V. McCollum



Paul Karrer



Otto Isler