Advanced Nutrition:
Micronutrients and Macronutrients

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Dietary Mineral

Dietary minerals are the chemical elements required by living organisms, other than the four elements carbon, hydrogen, nitrogen, and oxygen present in common organic molecules. The term "mineral" is archaic, since the intent of the definition is to describe chemical elements, not chemical compounds or actual minerals. Examples include calcium, magnesium, potassium, sodium, zinc, and iodine.

Dietitians may recommend that dietary elements are best supplied by ingesting specific foods rich with the chemical element(s) of interest. The elements may be naturally present in the food (e.g., calcium in dairy milk) or added to the food (e.g., orange juice fortified with calcium; iodized salt, salt fortified with iodine). Dietary supplements can be formulated to contain several different chemical elements (as compounds), a combination of vitamins and/or other chemical compounds, or a single element (as a compound or mixture of compounds), such as calcium (as carbonate, citrate, etc.) or magnesium (as oxide, etc.), chromium (usually as picolinate).

The dietary focus on chemical elements derives from an interest in supporting the biochemical reactions of metabolism with the required elemental components. Appropriate intake levels of certain chemical elements have been demonstrated to be required to maintain optimal health. Diet can meet all the body's chemical element requirements, although supplements can be used when some requirements (e.g., calcium, which is found mainly in dairy products) are not adequately met by the diet, or when chronic or acute deficiencies arise from pathology, injury, etc.

Essential chemical elements

Some sources state that sixteen chemical elements are *required* to support human biochemical processes by serving structural and functional roles as well as electrolytes: Most of the dietary elements are of relatively low atomic weight:

Periodic table highlighting dietary elements

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc		Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y		Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg							

*	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
**	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

The four organic basic elements	Quantity elements	Essential trace elements	Pervasive but no identified biological function in humans

The following play important roles in biological processes:

Dietary element	RDA/AI	Description	Category	Insufficiency	Excess
Potassium	4700 mg	Quantity	is a systemic electrolyte and is essential in coregulating ATP with sodium. Dietary sources include legumes, potato skin, tomatoes, and bananas.	hypokalemia	hyperkalemia
Chlorine	2300 mg	Quantity	is needed for production of hydrochloric acid in the stomach and in cellular pump functions. Table salt (sodium chloride) is the main dietary source.	hypochloremia	hyperchloremia
Sodium	1500 mg	Quantity	is a systemic electrolyte and is essential in coregulating ATP with potassium. Dietary sources	hyponatremia	hypernatremia

			include table salt (sodium chloride, the main source), sea vegetables, milk, and spinach.		
Calcium	1000 mg	Quantity	is needed for muscle, heart and digestive system health, builds bone, supports synthesis and function of blood cells. Dietary sources of calcium include dairy products, canned fish with bones (salmon, sardines), green leafy vegetables, nuts and seeds.	hypocalcaemia	hypercalcaemia
Phosphorus	700 mg	Quantity	is a component of bones, cells, in energy processing and many other functions. In biological contexts, usually seen as phosphate.	Hypophos-phatemia	Hyperphos-phatemia
Magnesium	420 mg	Quantity	is required for processing ATP and for bones. Dietary sources include nuts, soy beans, and cocoa mass.	Hypomagne-semia, magnesium deficiency	Hypermagne-semia
Zinc	11 mg	Trace	is pervasive and required for several enzymes such as carboxypeptidase, liver alcohol dehydrogenase, and carbonic anhydrase.	zinc deficiency	zinc toxicity
Iron	8 mg	Trace	is required for many proteins and enzymes, notably hemoglobin to prevent anemia. Dietary sources include red meat, leafy green	anaemia	iron overload disorder

			vegetables, fish (tuna, salmon), eggs, dried fruits, beans, whole grains, and enriched grains.		
Manganese	2.3 mg	Trace	is a cofactor in enzyme functions.	manganese deficiency	manganism
Copper	900 µg	Trace	is required component of many redox enzymes, including cytochrome c oxidase.	copper deficiency	copper toxicity
Iodine	150 µg	Trace	is required not only for the synthesis of thyroid hormones, thyroxine and triiodothyronine and to prevent goiter, but also, probably as an antioxidant, for extrathyroidal organs as mammary and salivary glands and for gastric mucosa and immune system (thymus): • Iodine in biology	iodine deficiency	iodism
Selenium	55 µg	Trace	a cofactor essential to activity of antioxidant enzymes like glutathione peroxidase.	selenium deficiency	selenosis
Molybd-enum	45 µg	Trace	the oxidases xanthine oxidase, aldehyde oxidase, and sulfite oxidase	molybdenum deficiency	

Other elements

Many elements have been suggested as essential, but such claims have usually not been confirmed. Definitive evidence for efficacy comes from the characterization of a biomolecule containing the element with an identifiable and testable function. One problem with identifying efficacy is that some elements are innocuous at low

concentrations and are pervasive, so proof of efficacy is lacking because deficiencies are difficult to reproduce.

Element	Description	Excess
Sulfur	Relatively large quantities of sulfur are required, but there is no RDA, as the sulfur is obtained from and used for amino acids, and therefore should be adequate in any diet containing enough protein.	(primarily associated with compounds)
Cobalt	Cobalt is required in the synthesis of vitamin B_{12}, but because bacteria are required to synthesize the vitamin, it is usually considered part of vitamin B_{12} deficiency rather than its own dietary element deficiency.	Cobalt poisoning
Nickel	There have been occasional studies asserting the essentiality of nickel, but it currently has no known RDA.	Nickel toxicity
Chromium	Chromium is sometimes described as essential. It is implicated in sugar metabolism in humans, leading to a market for the supplement chromium picolinate, but definitive biochemical evidence for a physiological function is lacking.	Chromium toxicity
Fluorine	Fluorine (as fluoride) has been described as conditionally essential, depending upon the importance placed upon the prevention of chronic disease.	Fluoride poisoning
Boron	Boron has been found to be essential for the utilization of vitamin D and calcium in the body.	
Other	Arsenic, bromine, cadmium, silicon, tungsten, and vanadium have established, albeit specialized, biochemical roles as structural or functional cofactors in other organisms. These elements appear not to be utilized by humans.	Multiple

Chapter- 2

Calcium

Appearance
Dull gray, silver

Spectral lines of Calcium

General properties	
Name, symbol, number	calcium, Ca, 20
Element category	alkaline earth metal
Group, period, block	2, 4, s
Standard atomic weight	40.078g·mol^{-1}
Electron configuration	[Ar] 4s^2
Electrons per shell	2, 8, 8, 2 (Image)

Physical properties	
Phase	solid
Density (near r.t.)	1.55 g·cm^{-3}
Liquid density at m.p.	1.378 g·cm^{-3}
Melting point	1115 K842 ° ,C1548 ° ,F
Boiling point	1757 K1484 ° ,C2703 ° ,F
Heat of fusion	8.54 kJ·mol^{-1}
Heat of vaporization	154.7 kJ·mol^{-1}
Specific heat capacity	(25 °C) 25.929 J·mol^{-1}·K^{-1}

Vapor pressure

P (Pa)	1	10	100	1 k	10 k	100 k
at T (K)	864	956	1071	1227	1443	1755

Atomic properties

Oxidation states	**+2**, +1 (strongly basic oxide)
Electronegativity	1.00 (Pauling scale)
Ionization energies (more)	1st: 589.8 kJ·mol^{-1} 2nd: 1145.4 kJ·mol^{-1} 3rd: 4912.4 kJ·mol^{-1}
Atomic radius	197 pm
Covalent radius	176±10 pm
Van der Waals radius	231 pm

Miscellanea

Crystal structure	face-centered cubic
Magnetic ordering	diamagnetic
Electrical resistivity	(20 °C) 33.6 nΩ·m
Thermal conductivity	(300 K) 201 W·m^{-1}·K^{-1}
Thermal expansion	(25 °C) 22.3 µm·m^{-1}·K^{-1}
Speed of sound (thin rod)	(20 °C) 3810 m/s
Young's modulus	20 GPa
Shear modulus	7.4 GPa
Bulk modulus	17 GPa
Poisson ratio	0.31
Mohs hardness	1.75
Brinell hardness	167 MPa
CAS registry number	7440-70-2

Most stable isotopes

iso	NA	half-life	DM	DE (MeV)	DP
^{40}Ca	96.941%	^{40}Ca is stable with 20 neutrons			
^{41}Ca	trace	1.03×10^{5} y	ε	-	^{41}K
^{42}Ca	0.647%	^{42}Ca is stable with 22 neutrons			
^{43}Ca	0.135%	^{43}Ca is stable with 23 neutrons			
^{44}Ca	2.086%	^{44}Ca is stable with 24 neutrons			
^{45}Ca	syn	162.7 d	β$^-$	0.258	^{45}Sc
^{46}Ca	0.004%	>2.8×10^{15} y	β$^-$β$^-$	?	^{46}Ti
^{47}Ca	syn	4.536 d	β$^-$ γ	0.694, 1.99 1.297	^{47}Sc -
^{48}Ca	0.187%	>4×10^{19} y	β$^-$β$^-$	?	^{48}Ti

Calcium is the chemical element with the symbol **Ca** and atomic number 20. It has an atomic mass of 40.078 amu. Calcium is a soft gray alkaline earth metal, and is the fifth most abundant element by mass in the Earth's crust. Calcium is also the fifth most abundant dissolved ion in seawater by both molarity and mass, after sodium, chloride, magnesium, and sulfate.

Calcium is essential for living organisms, particularly in cell physiology, where movement of the calcium ion Ca^{2+} into and out of the cytoplasm functions as a signal for many cellular processes. As a major material used in mineralization of bones and shells, calcium is the most abundant metal by mass in many animals.

Notable characteristics

Flame test. Brick red color originates from calcium

Chemically calcium is reactive and soft for a metal (though harder than lead, it can be cut with a knife with difficulty). It is a silvery metallic element that must be extracted by electrolysis from a fused salt like calcium chloride. Once produced, it rapidly forms a gray-white oxide and nitride coating when exposed to air. In bulk-form (typically as chips

or "turnings") the metal is somewhat difficult to ignite, more so even than magnesium chips; but when lit, the metal burns in air with a brilliant high-intensity red light. Calcium metal reacts with water, evolving hydrogen gas at a rate rapid enough to be noticeable, but not fast enough at room temperature to generate much heat. In powdered form, however, the reaction with water is extremely rapid, as the increased surface area of the powder accelerates the reaction with the water. Part of the slowness of the calcium-water reaction results from the metal being partly protected by insoluble white calcium hydroxide. In water solutions of acids, where this salt is soluble, calcium reacts vigorously.

Calcium, with a density of 1.55 g/cm^3, is the lightest of the alkaline earth metals; magnesium (specific gravity 1.74) and beryllium (1.84) are more dense, although lighter in atomic mass. From strontium onward, the alkali earth metals become more dense with increasing atomic mass.

It has two allotropes.

Calcium has a higher electrical resistivity than copper or aluminium, yet weight-for-weight, due to its much lower density, it is a rather better conductor than either. However, its use in terrestrial applications is usually limited by its high reactivity with air.

Calcium salts are colorless from any contribution of the calcium, and ionic solutions of calcium (Ca^{2+}) are colorless as well. Many calcium salts are not soluble in water. When in solution, the calcium ion to the human taste varies remarkably, being reported as mildly salty, sour, "mineral like" or even "soothing." It is apparent that many animals can taste, or develop a taste, for calcium, and use this sense to detect the mineral in salt licks or other sources. In human nutrition, soluble calcium salts may be added to tart juices without much effect to the average palate.

Calcium is the fifth most abundant element by mass in the human body, where it is a common cellular ionic messenger with many functions, and serves also as a structural element in bone. It is the relatively high atomic-numbered calcium in the skeleton which causes bone to be radio-opaque. Of the human body's solid components after drying and burning of organics (as for example, after cremation), about a third of the total "mineral" mass remaining, is the approximately one kilogram of calcium which composes the average skeleton (the remainder being mostly phosphorus and oxygen).

H and K lines

Visible spectra of many stars, including the Sun, exhibit strong absorption lines of singly ionized calcium. Prominent among these are the H-line at 3968.5 Å and the K line at 3933.7 Å of singly ionized calcium, or Ca II. For the Sun and stars with low temperatures, the prominence of the H and K lines can be an indication of strong magnetic activity in the chromosphere. Measurement of periodic variations of these active regions can also be used to deduce the rotation periods of these stars.

Compounds

Calcium, combined with phosphate to form hydroxylapatite, is the mineral portion of human and animal bones and teeth. The mineral portion of some corals can also be transformed into hydroxylapatite.

Calcium hydroxide (slaked lime) is used in many chemical refinery processes and is made by heating limestone at high temperature (above 825 °C) and then carefully adding water to it. When lime is mixed with sand, it hardens into a mortar and is turned into plaster by carbon dioxide uptake. Mixed with other compounds, lime forms an important part of Portland cement.

Calcium carbonate ($CaCO_3$) is one of the common compounds of calcium. It is heated to form quicklime (CaO), which is then added to water (H_2O). This forms another material known as slaked lime ($Ca(OH)_2$), which is an inexpensive base material used throughout the chemical industry. Chalk, marble, and limestone are all forms of calcium carbonate.

When water percolates through limestone or other soluble carbonate rocks, it partially dissolves the rock and causes cave formation and characteristic stalactites and stalagmites and also forms hard water. Other important calcium compounds are calcium nitrate, calcium sulfide, calcium chloride, calcium carbide, calcium cyanamide and calcium hypochlorite.

A few calcium compounds in the oxidation state +1 have also been investigated recently.

Nucleosynthesis

Stable Calcium is created in extremely large, extremely hot (over 2.5 billion kelvin) stars. It requires one atom of argon and one atom of helium.

Isotopes

Calcium has four stable isotopes (^{40}Ca and ^{42}Ca through ^{44}Ca), plus two more isotopes (^{46}Ca and ^{48}Ca) that have such long half-lives that for all practical purposes they can be considered stable. The 20% range in relative mass among naturally occurring calcium isotopes is greater than for any element except hydrogen and helium. Calcium also has a cosmogenic isotope, radioactive ^{41}Ca, which has a half-life of 103,000 years. Unlike cosmogenic isotopes that are produced in the atmosphere, ^{41}Ca is produced by neutron activation of ^{40}Ca. Most of its production is in the upper metre or so of the soil column, where the cosmogenic neutron flux is still sufficiently strong. ^{41}Ca has received much attention in stellar studies because it decays to ^{41}K, a critical indicator of solar-system anomalies.

97% of naturally occurring calcium is in the form of ^{40}Ca. ^{40}Ca is one of the daughter products of ^{40}K decay, along with ^{40}Ar. While K-Ar dating has been used extensively in the geological sciences, the prevalence of ^{40}Ca in nature has impeded its use in dating.

Techniques using mass spectrometry and a double spike isotope dilution have been used for K-Ca age dating.

The most abundant isotope, ^{40}Ca, has a nucleus of 20 protons and 20 neutrons. This is the heaviest stable isotope of any element which has equal numbers of protons and neutrons. In supernova explosions, calcium is formed from the reaction of carbon with various numbers of alpha particles (helium nuclei), until the most common calcium isotope (containing 10 helium nuclei) has been synthesized.

Isotope fractionation

As with the isotopes of other elements, a variety of processes fractionate, or alter the relative abundance of, calcium isotopes. The best studied of these processes is the mass dependent fractionation of calcium isotopes that accompanies the precipitation of calcium minerals, such as calcite, aragonite and apatite, from solution. Isotopically light calcium is preferentially incorporated into minerals, leaving the solution from which the mineral precipitated enriched in isotopically heavy calcium. At room temperature the magnitude of this fractionation is roughly 0.25‰ (0.025%) per atomic mass unit (AMU). Mass-dependant differences in calcium isotope composition conventionally are expressed the ratio of two isotopes (usually $^{44}Ca/^{40}Ca$) in a sample compared to the same ratio in a standard reference material. $^{44}Ca/^{40}Ca$ varies by about 1% among common earth materials.

Calcium isotope fractionation during mineral formation has led to several applications of calcium isotopes. In particular, the 1997 observation by Skulan and DePaolo that calcium minerals are isotopically lighter than the solutions from which the minerals precipitate is the basis of analogous applications in medicine and in paleooceanography. In animals with skeletons mineralized with calcium the calcium isotopic composition of soft tissues reflects the relative rate of formation and dissolution of skeletal mineral. In humans changes in the calcium isotopic composition of urine have been shown to be related to changes in bone mineral balance. When the rate of bone formation exceeds the rate of bone resorption, soft tissue $^{44}Ca/^{40}Ca$ rises. Soft tissue $^{44}Ca/^{40}Ca$ falls when bone resorption exceeds bone formation. Because of this relationship, calcium isotopic measurements of urine or blood may be useful in the early detection of metabolic bone diseases like osteoporosis.

A similar system exists in the ocean, where seawater $^{44}Ca/^{40}Ca$ tends to rise when the rate of removal of Ca^{2+} from seawater by mineral precipitation exceeds the input of new calcium into the ocean, and fall when calcium input exceeds mineral precipitation. It follows that rising $^{44}Ca/^{40}Ca$ corresponds to falling seawater Ca^{2+} concentration, and falling $^{44}Ca/^{40}Ca$ corresponds to rising seawater Ca^{2+} concentration. In 1997 Skulan and DePaolo presented the first evidence of change in seawater $^{44}Ca/^{40}Ca$ over geologic time, along with a theoretical explanation of these changes. More recent papers have confirmed this observation, demonstrating that seawater Ca^{2+} concentration is not constant, and that the ocean probably never is in "steady state" with respect to its calcium input and output.

This has important climatological implications, as the marine calcium cycle is closely tied to the carbon cycle (see below).

Geochemical cycling

Calcium provides an important link between tectonics, climate and the carbon cycle. In the simplest terms, uplift of mountains exposes Ca-bearing rocks to chemical weathering and releases Ca^{2+} into surface water. This Ca^{2+} eventually is transported to the ocean where it reacts with dissolved CO_2 to form limestone. Some of this limestone settles to the sea floor where it is incorporated into new rocks. Dissolved CO_2, along with carbonate and bicarbonate ions, are referred to as dissolved inorganic carbon (DIC).

Travertine terraces Pamukkale, Turkey

The actual reaction is more complicated and involves the bicarbonate ion (HCO_3^-) that forms when CO_2 reacts with water at seawater pH:

$$Ca^{2+} + 2HCO_3^- \rightarrow CaCO_3 \text{ (limestone)} + CO_2 + H_2O$$

Note that at ocean pH most of the CO_2 produced in this reaction is immediately converted back into $HCO3^-$. The reaction results in a net transport of one molecule of CO_2 from the ocean/atmosphere into the lithosphere.

The result is that each Ca^{2+} ion released by chemical weathering ultimately removes one CO_2 molecule from the surficial system (atmosphere, ocean, soils and living organisms), storing it in carbonate rocks where it is likely to stay for hundreds of millions of years. The weathering of calcium from rocks thus scrubs CO_2 from the ocean and atmosphere, exerting a strong long-term effect on climate. Analogous cycles involving magnesium, and to a much smaller extent strontium and barium, have the same effect.

As the weathering of limestone ($CaCO_3$) liberates equimolar amounts of Ca^{2+} and CO_2, it has no net effect on the CO_2 content of the atmosphere and ocean. The weathering of silicate rocks like granite, on the other hand, is a net CO2 sink because it produces abundant Ca^{2+} but very little CO_2.

Occurrence

Calcium is not naturally found in its elemental state. Calcium occurs most commonly in sedimentary rocks in the minerals calcite, dolomite and gypsum. It also occurs in igneous and metamorphic rocks chiefly in the silicate minerals: plagioclase, amphiboles, pyroxenes and garnets

Applications

Calcium is used

- as a reducing agent in the extraction of other metals, such as uranium, zirconium, and thorium.
- as a deoxidizer, desulfurizer, or decarbonizer for various ferrous and nonferrous alloys.
- as an alloying agent used in the production of aluminium, beryllium, copper, lead, and magnesium alloys.
- in the making of cements and mortars to be used in construction.
- in the making of cheese, where calcium ions influence the activity of rennin in bringing about the coagulation of milk.

Calcium compounds

- Calcium carbonate ($CaCO_3$) is used in manufacturing cement and mortar, lime, limestone (usually used in the steel industry) and aids in production in the glass industry. It also has chemical and optical uses as mineral specimens in toothpastes, for example.
- Calcium hydroxide solution ($Ca(OH)_2$) (also known as limewater) is used to detect the presence of carbon dioxide by being bubbled through a solution. It turns cloudy where CO_2 is present.
- Calcium arsenate ($Ca_3(AsO_4)_2$) is used in insecticides.
- Calcium carbide (CaC_2) is used to make acetylene gas (for use in acetylene torches for welding) and in the manufacturing of plastics.

- Calcium chloride ($CaCl_2$) is used in ice removal and dust control on dirt roads, in conditioner for concrete, as an additive in canned tomatoes, and to provide body for automobile tires.
- Calcium cyclamate ($Ca(C_6H_{11}NHSO_3)_2$) was used as a sweetening agent but is no longer permitted for use because of suspected cancer-causing properties.
- Calcium gluconate ($Ca(C_6H_{11}O_7)_2$) is used as a food additive and in vitamin pills.
- Calcium hypochlorite ($Ca(OCl)_2$) is used as a swimming pool disinfectant, as a bleaching agent, as an ingredient in deodorant, and in algaecide and fungicide.
- Calcium permanganate ($Ca(MnO_4)_2$) is used in liquid rocket propellant, textile production, as a water sterilizing agent and in dental procedures.
- Calcium phosphate ($Ca_3(PO_4)_2$) is used as a supplement for animal feed, fertilizer, in commercial production for dough and yeast products, in the manufacture of glass, and in dental products.
- Calcium phosphide (Ca_3P_2) is used in fireworks, rodenticide, torpedoes and flares.
- Calcium stearate ($Ca(C_{18}H_{35}O_2)_2$) is used in the manufacture of wax crayons, cements, certain kinds of plastics and cosmetics, as a food additive, in the production of water resistant materials and in the production of paints.
- Calcium sulfate ($CaSO_4 \cdot 2H_2O$) is used as common blackboard chalk, as well as, in its hemihydrate form better known as Plaster of Paris.
- Calcium tungstate ($CaWO_4$) is used in luminous paints, fluorescent lights and in X-ray studies.
- Hydroxylapatite ($Ca_5(PO_4)_3(OH)$, but is usually written $Ca_{10}(PO_4)_6(OH)_2$) makes up seventy percent of bone. Also carbonated-calcium deficient hydroxylapatite is the main mineral of which dental enamel and dentin are comprised.

Nutrition

Recommended adequate intake by the IOM for calcium:

Age	Calcium (mg/day)
0–6 months	210
7–12 months	270
1–3 years	500
4–8 years	800
9–18 years	1300
19–50 years	1000
51+ years	1200

Calcium is an important component of a healthy diet and a mineral necessary for life. The National Osteoporosis Foundation says, "Calcium plays an important role in building stronger, denser bones early in life and keeping bones strong and healthy later in life." Approximately 99 percent of the body's calcium is stored in the bones and teeth. The rest of the calcium in the body has other important uses, such as some exocytosis, especially neurotransmitter release, and muscle contraction. In the electrical conduction system of the heart, calcium replaces sodium as the mineral that depolarizes the cell, proliferating

the action potential. In cardiac muscle, sodium influx commences an action potential, but during potassium efflux, the cardiac myocyte experiences calcium influx, prolonging the action potential and creating a plateau phase of dynamic equilibrium. Long-term calcium deficiency can lead to rickets and poor blood clotting and in case of a menopausal woman, it can lead to osteoporosis, in which the bone deteriorates and there is an increased risk of fractures. While a lifelong deficit can affect bone and tooth formation, over-retention can cause hypercalcemia (elevated levels of calcium in the blood), impaired kidney function and decreased absorption of other minerals. High calcium intakes or high calcium absorption were previously thought to contribute to the development of kidney stones. However, a high calcium intake has been associated with a lower risk for kidney stones in more recent research. Vitamin D is needed to absorb calcium.

Dairy products, such as milk and cheese, are a well-known source of calcium. Some individuals are allergic to dairy products and even more people, particularly those of non Indo-European descent, are lactose-intolerant, leaving them unable to consume non-fermented dairy products in quantities larger than about half a liter per serving. Others, such as vegans, avoid dairy products for ethical and health reasons. Fortunately, many good sources of calcium exist. These include seaweeds such as kelp, wakame and hijiki; nuts and seeds (like almonds and sesame); blackstrap molasses; beans; figs; quinoa; amaranth; collard greens; okra; rutabaga; broccoli; dandelion leaves; kale; and fortified products such as orange juice and soy milk. An overlooked source of calcium is eggshell, which can be ground into a powder and mixed into food or a glass of water. Cultivated vegetables generally have less calcium than wild plants.

The calcium content of most foods can be found in the USDA National Nutrient Database.

Dietary calcium supplements

500 milligram calcium supplements made from calcium carbonate

Calcium supplements are used to prevent and to treat calcium deficiencies. Most experts recommend that supplements be taken with food and that no more than 600 mg should be taken at a time because the percent of calcium absorbed decreases as the amount of calcium in the supplement increases. It is recommended to spread doses throughout the day. Recommended daily calcium intake for adults ranges from 1000 to 1500 mg. It is recommended to take supplements with food to aid in absorption.

Vitamin D is added to some calcium supplements. Proper vitamin D status is important because vitamin D is converted to a hormone in the body which then induces the synthesis of intestinal proteins responsible for calcium absorption.

- The absorption of calcium from most food and commonly used dietary supplements is very similar. This is contrary to what many calcium supplement manufacturers claim in their promotional materials.
- Milk is an excellent source of dietary calcium for those whose bodies tolerate it because it has a high concentration of calcium and the calcium in milk is excellently absorbed.
- Soymilk and other vegetable milks are usually sold with calcium added so that their calcium concentration is as high as in milk
- Also different kind of juices boosted with calcium are widely available.
- Calcium carbonate is the most common and least expensive calcium supplement. It should be taken with food. It depends on low pH levels for proper absorption in the intestine. Some studies suggests that the absorption of calcium from calcium carbonate is similar to the absorption of calcium from milk. While most people digest calcium carbonate very well, some might develop gastrointestinal discomfort or gas. Taking magnesium with it can help to avoid constipation. Calcium carbonate is 40% elemental calcium. 1000 mg will provide 400 mg of calcium. However, supplement labels will usually indicate how much calcium is present in each serving, not how much calcium carbonate is present.
- Antacids frequently contain calcium carbonate, and are a commonly used, inexpensive calcium supplement
- Coral calcium is a salt of calcium derived from fossilized coral reefs. Coral calcium is composed of calcium carbonate and trace minerals.
- Calcium citrate can be taken without food and is the supplement of choice for individuals with achlorhydria or who are taking histamine-2 blockers or proton-pump inhibitors. It is more easily digested and absorbed than calcium carbonate if taken on an empty stomach and less likely to cause constipation and gas than calcium carbonate. It also has a lower risk of contributing to the formation of kidney stones. Calcium citrate is about 21% elemental calcium. 1000 mg will provide 210 mg of calcium. It is more expensive than calcium carbonate and more of it must be taken to get the same amount of calcium.
- Calcium phosphate costs more than calcium carbonate, but less than calcium citrate. It is easily absorbed and is less likely to cause constipation and gas than either.

- Calcium lactate has similar absorption as calcium carbonate, but is more expensive. Calcium lactate and calcium gluconate are less concentrated forms of calcium and are not practical oral supplements.
- Calcium chelates are synthetic calcium compounds, with calcium bound to an organic molecule, such as malate, aspartate, or fumarate. These forms of calcium may be better absorbed on an empty stomach. However, in general they are absorbed similarly to calcium carbonate and other common calcium supplements when taken with food. The 'chelate' mimics the action that natural food performs by keeping the calcium soluble in the intestine. Thus, on an empty stomach, in some individuals, chelates might theoretically be absorbed better.
- Microcrystalline hydroxyapatite (MH) is marketed as a calcium supplement, and has in some randomized trials been found to be more effective than calcium carbonate.

In July 2006, a report citing research from Fred Hutchinson Cancer Research Center in Seattle, Washington claimed that women in their 50s gained 5 pounds less in a period of 10 years by taking more than 500 mg of calcium supplements than those who did not. However, the doctor in charge of the study, Dr. Alejandro J. Gonzalez also noted it would be "going out on a limb" to suggest calcium supplements as a weight-limiting aid.

Prevention of fractures due to osteoporosis

Such studies often do not test calcium alone, but rather combinations of calcium and vitamin D. Randomized controlled trials found both positive and negative effects. The different results may be explained by doses of calcium and underlying rates of calcium supplementation in the control groups. However, it is clear that increasing the intake of calcium promotes deposition of calcium in the bones, where it is of more benefit in preventing the compression fractures resulting from the osteoporotic thinning of the dendritic web of the bodies of the vertebrae, than it is at preventing the more serious cortical bone fractures which happen at hip and wrist.

Possible cancer prevention

A meta-analysis by the international Cochrane Collaboration of two randomized controlled trials found that calcium "might contribute to a moderate degree to the prevention of adenomatous colonic polyps".

More recent studies were conflicting, and one which was positive for effect (Lappe, et al.) did control for a possible anti-carcinogenic effect of vitamin D, which was found to be an independent positive influence from calcium-alone on cancer risk (see second study below).

- A randomized controlled trial found that 1000 mg of elemental calcium and 400 IU of vitamin D_3 had no effect on colorectal cancer
- A randomized controlled trial found that 1400–1500 mg supplemental calcium and 1100 IU vitamin D_3 reduced aggregated cancers with a relative risk of 0.402.

- An observational cohort study found that high calcium and vitamin D intake was associated with "lower risk of developing premenopausal breast cancer."

Hazards and toxicity

Compared to other metals, the calcium ion and most calcium compounds have low toxicity. This is not surprising given the very high natural abundance of calcium compounds in the environment and in organisms. Calcium poses few, if any, serious environmental problems. Acute calcium poisoning is rare, and difficult to achieve unless calcium compounds are administered intravenously. For example, the oral median lethal dose (LD^{50}) for rats for calcium carbonate and calcium chloride are 6.45 and 1.4 g/kg, respectively.

Calcium metal is hazardous because of its sometimes violent reactions with water and acids. Calcium metal is found in some drain cleaners, where it functions to generate heat and calcium hydroxide that saponifies the fats and liquefies the proteins (e.g., hair) that block drains. When swallowed calcium metal has the same effect on the mouth, esophagus and stomach, and can be fatal.

Excessive consumption of calcium carbonate antacids/dietary supplements (such as Tums) over a period of weeks or months can cause milk-alkali syndrome, with symptoms ranging from hypercalcemia to potentially fatal renal failure. What constitutes “excessive” consumption is not well known and probably varies a great deal from person to person. Persons who consume more than 10 grams/day of $CaCO_3$ (=4 g Ca) are at risk of developing milk-alkali syndrome, but the condition has been reported in at least one person consuming only 2.5 grams/day of $CaCO_3$ (=1 g Ca), an amount usually considered moderate and safe.

Chapter- 3

Iron

Appearance
lustrous metallic with a grayish tinge

Spectral lines of Iron

General properties	
Name, symbol, number	iron, Fe, 26
Element category	transition metal
Group, period, block	8, 4, d
Standard atomic weight	55.845g·mol^{-1}
Electron configuration	[Ar] 3d^6 4s^2
Electrons per shell	2, 8, 14, 2 (Image)

Physical properties	
Phase	solid
Density (near r.t.)	7.874 g·cm^{-3}
Liquid density at m.p.	6.98 g·cm^{-3}
Melting point	1811 K1538 ° ,C2800 ° ,F
Boiling point	3134 K2862 ° ,C5182 ° ,F
Heat of fusion	13.81 kJ·mol^{-1}
Heat of vaporization	340 kJ·mol^{-1}
Specific heat capacity	(25 °C) 25.10 J·mol^{-1}·K^{-1}

Vapor pressure

P (Pa)	1	10	100	1 k	10 k	100 k
at T (K)	1728	1890	2091	2346	2679	3132

Atomic properties

Electronegativity	1.83 (Pauling scale)
Ionization energies (more)	1st: 762.5 kJ·mol^{-1} 2nd: 1561.9 kJ·mol^{-1} 3rd: 2957 kJ·mol^{-1}
Atomic radius	126 pm
Covalent radius	132±3 (low spin), 152±6 (high spin) pm
Miscellanea	
Crystal structure	body-centered cubic
Magnetic ordering	ferromagnetic
	1043 K
Electrical resistivity	(20 °C) 96.1 nΩ·m
Thermal conductivity	(300 K) 80.4 W·m^{-1}·K^{-1}
Thermal expansion	(25 °C) 11.8 µm·m^{-1}·K^{-1}
Speed of sound (thin rod)	(r.t.) (electrolytic) 5120 m·s^{-1}
Young's modulus	211 GPa
Shear modulus	82 GPa
Bulk modulus	170 GPa
Poisson ratio	0.29
Mohs hardness	4
Vickers hardness	608 MPa
Brinell hardness	490 MPa
CAS registry number	7439-89-6

Most stable isotopes

iso	NA	half-life	DM	DE (MeV)	DP
^{54}Fe	5.8%	>3.1×10^{22}y	2ε capture	?	^{54}Cr
^{55}Fe	syn	2.73 y	ε capture	0.231	^{55}Mn
^{56}Fe	91.72%	^{56}Fe is stable with 30 neutrons			
^{57}Fe	2.2%	^{57}Fe is stable with 31 neutrons			
^{58}Fe	0.28%	^{58}Fe is stable with 32 neutrons			
^{59}Fe	syn	44.503 d	β^-	1.565	^{59}Co
^{60}Fe	syn	2.6×10^{6} y	β^-	3.978	^{60}Co

Iron is a chemical element with the symbol **Fe** (Latin: *ferrum*) and atomic number 26. It is a metal in the first transition series. It is the most common element in the whole planet Earth, forming much of Earth's outer and inner core, and it is the fourth most common element in the Earth's crust. It is produced in abundance as a result of fusion in high-mass stars, where the production of nickel-56 (which decays to iron) is the last nuclear fusion reaction that is exothermic, becoming the last element to be produced before collapse of a supernova leads to events that scatter the precursor radionuclides of iron into space.

Like other Group 8 elements, iron exists in a wide range of oxidation states, −2 to + 6, although +2 and +3 are the most common. Elemental iron occurs in meteoroids and other low oxygen environments, but is reactive to oxygen and water. Fresh iron surfaces appear lustrous silvery-gray, but oxidize in normal air to give iron oxides, also known as rust. Unlike many other metals which form passivating oxide layers, iron oxides occupy more volume than iron metal, and thus iron oxides flake off and expose fresh surfaces for corrosion.

Iron metal has been used since ancient times, though lower-melting copper alloys were used first in history. Pure iron is soft (softer than aluminium), but is unobtainable by smelting. The material is significantly hardenened and strengthened by impurities from the smelting process, such as carbon. A certain proportion of carbon (between 0.2% and 2.1%) produces steel, which may be up to 1000 times harder than pure iron. Crude iron metal is produced in blast furnaces, where ore is reduced by coke to cast iron. Further refinement with oxygen reduces the carbon content to make steel. Steels and low carbon iron alloys with other metals (alloy steels) are by far the most common metals in industrial use, due to their great range of desirable properties.

Iron chemical compounds, which include ferrous and ferric compounds, have many uses. Iron oxide mixed with aluminium powder can be ignited to create a thermite reaction, used in welding and purifying ores. It forms binary compounds with the halogens and the chalcogens. Among its organometallic compounds, ferrocene was the first sandwich compound discovered.

Iron plays an important role in biology, forming complexes with molecular oxygen in hemoglobin and myoglobin; these two compounds are common oxygen transport proteins in vertebrates. Iron is also the metal used at the active site of many important redox enzymes dealing with cellular respiration and oxidation and reduction in plants and animals.

Characteristics

Mechanical properties

Characteristic values of tensile strength (TS) and Brinell hardness (BH) of different forms of iron.

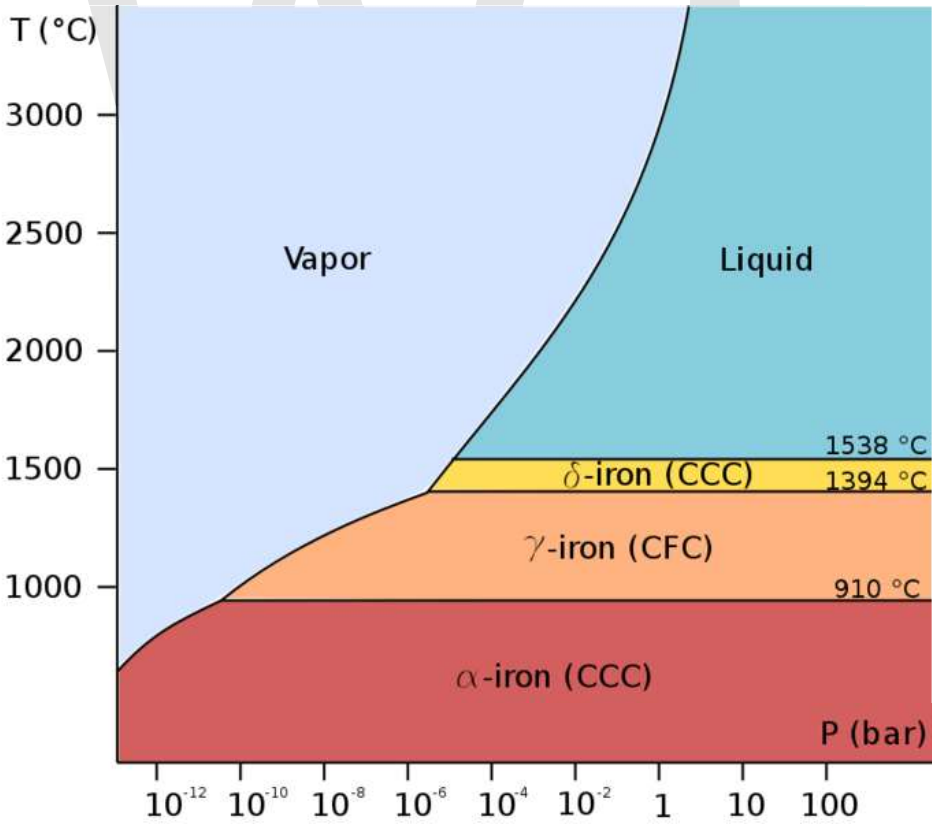
Material	TS (MPa)	BH (Brinell)
Iron whiskers	11000	
Ausformed (hardened) steel	2930	850–1200
Martensitic steel	2070	600
Bainitic steel	1380	400
Pearlitic steel	1200	350
Cold-worked iron	690	200

Small-grain iron	340	100
Carbon-containing iron	140	40
Pure, single-crystal iron	10	3

Mechanical properties of iron and its alloys are evaluated using a variety of tests, such as the Brinell test, Rockwell test, or tensile strength tests, among others; the results on iron are so consistent that iron is often used to calibrate measurements or to relate the results of one test to another. Those measurements reveal that mechanical properties of iron crucially depend on purity: Purest research-purpose single crystals of iron are softer than aluminium. Addition of only 10 parts per million of carbon doubles their strength. The hardness increases rapidly with carbon content up to 0.2% and saturates at ~0.6%. The purest industrially produced iron (about 99.99% purity) has a hardness of 20–30 Brinell.

Phase diagram and allotropes

Iron represents an example of allotropy in a metal. There are at least four allotropic forms of iron, known as α, γ, δ, and ε; at very high pressures, some controversial experimental evidence exists for a phase β stable at very high pressures and temperatures.



Low-pressure phase diagram of pure iron

As molten iron cools down it crystallizes at 1538 °C into its δ allotrope, which has a body-centered cubic (bcc) crystal structure. As it cools further its crystal structure changes to face-centered cubic (fcc) at 1394 °C, when it is known as γ-iron, or austenite. At 912 °C the crystal structure again becomes bcc as α-iron, or ferrite, is formed, and at 770 °C (the Curie point, T_c) iron becomes magnetic. As the iron passes through the Curie temperature there is no change in crystalline structure, but there is a change in "domain structure", where each domain contains iron atoms with a particular electronic spin. In unmagnetized iron, all the electronic spins of the atoms within one domain are in the same direction; the neighboring domains point in various directions and thus cancel out. In magnetized iron, the electronic spins of all the domains are aligned, so that the magnetic effects of neighboring domains reinforce each other. Although each domain contains billions of atoms, they are very small, about 10 micrometres across.. At pressures above approximately 10 GPa and temperatures of a few hundred kelvin or less, α-iron changes into a hexagonal close-packed (hcp) structure, which is also known as ε-iron; the higher-temperature γ-phase also changes into ε-iron, but does so at higher pressure. The β-phase, if it exists, would appear at pressures of at least 50 GPa and temperatures of at least 1500 K; it has been thought to have an orthorhombic or a double hcp structure.

Iron is of greatest importance when mixed with certain other metals and with carbon to form steels. There are many types of steels, all with different properties, and an understanding of the properties of the allotropes of iron is key to the manufacture of good quality steels.

α-iron, also known as ferrite, is the most stable form of iron at normal temperatures. It is a fairly soft metal that can dissolve only a small concentration of carbon (no more than 0.021% by mass at 910 °C).

Above 912 °C and up to 1400 °C α-iron undergoes a phase transition from bcc to the fcc configuration of γ-iron, also called austenite. This is similarly soft and metallic but can dissolve considerably more carbon (as much as 2.04% by mass at 1146 °C). This form of iron is used in the type of stainless steel used for making cutlery, and hospital and food-service equipment.

The high-pressure phases of iron are important as endmember models for the solid parts of planetary cores. The inner core of the Earth is generally assumed to consist essentially of an iron-nickel alloy with ε (or β) structure.

The melting point of iron is experimentally well constrained for pressures up to approximately 50 GPa. For higher pressures, different studies placed the γ-ε-liquid triple point at pressures differing by tens of gigapascals and yielded differences of more than 1000 K for the melting point. Generally speaking, molecular dynamics computer simulations of iron melting and shock wave experiments suggest higher melting points and a much steeper slope of the melting curve than static experiments carried out in diamond anvil cells.

Isotopes

Naturally occurring iron consists of four stable isotopes: 5.845% of ^{54}Fe, 91.754% of ^{56}Fe, 2.119% of ^{57}Fe and 0.282% of ^{58}Fe. The nuclide ^{54}Fe is predicted to undergo double beta decay, but this process had never been observed experimentally for these nuclei, and only the lower limit on the half-life was established: $t_{1/2}>3.1\times10^{22}$ years. ^{60}Fe is an extinct radionuclide of long half-life (2.6 million years).

Much of the past work on measuring the isotopic composition of Fe has focused on determining ^{60}Fe variations due to processes accompanying nucleosynthesis (i.e., meteorite studies) and ore formation. In the last decade however, advances in mass spectrometry technology have allowed the detection and quantification of minute, naturally occurring variations in the ratios of the stable isotopes of iron. Much of this work has been driven by the Earth and planetary science communities, although applications to biological and industrial systems are beginning to emerge.

The most abundant iron isotope ^{56}Fe is of particular interest to nuclear scientists as it represents the most stable nuclide possible. It is impossible to perform fission or fusion on ^{56}Fe and still liberate energy. Since ^{56}Ni is easily produced from lighter nuclei in the alpha process in nuclear reactions in supernovae, nickel-56 (14 alpha particles) is the endpoint of fusion chains inside extremely massive stars, since addition of another alpha particle would result in zinc-60, which requires a great deal more energy. This nickel-56, which has a half-life of about 6 days, is therefore made in quantity in these stars, but soon decays by two successive positron emissions within supernova decay products in the supernova remnant gas cloud, to first radioactive cobalt-56, and then stable iron-56. This last nuclide is therefore common in the universe, relative to other stable metals of approximately the same atomic weight.

In phases of the meteorites *Semarkona* and *Chervony Kut* a correlation between the concentration of ^{60}Ni, the daughter product of ^{60}Fe, and the abundance of the stable iron isotopes could be found which is evidence for the existence of ^{60}Fe at the time of formation of the solar system. Possibly the energy released by the decay of ^{60}Fe contributed, together with the energy released by decay of the radionuclide ^{26}Al, to the remelting and differentiation of asteroids after their formation 4.6 billion years ago. The abundance of ^{60}Ni present in extraterrestrial material may also provide further insight into the origin of the solar system and its early history. Of the stable isotopes, only ^{57}Fe has a nuclear spin ($-1/2$).

Nuclei of iron atoms have some of the highest binding energies per nucleon, surpassed only by the nickel isotope ^{62}Ni. This is formed by nuclear fusion in stars. Although a further tiny energy gain could be extracted by synthesizing ^{62}Ni, conditions in stars are unsuitable for this process to be favored. Elemental distribution on Earth greatly favors iron over nickel, and also presumably in supernova element production.

Iron-56 is the heaviest stable isotope produced by the alpha process in stellar nucleosynthesis; elements heavier than iron and nickel require a supernova for their

formation. Iron is the most abundant element in the core of red giants, and is the most abundant metal in iron meteorites and in the dense metal cores of planets such as Earth.

Nucleosynthesis

Iron is created by extremely large, extremely hot (over 2.5 billion kelvin) stars, through a process called the silicon burning process. It is the heaviest stable element to be produced in this manner. The process starts with the second largest stable nucleus created by silicon burning: calcium. One stable nucleus of calcium fuses with one helium nucleus, creating unstable titanium. Before the titanium decays, it can fuse with another helium nucleus, creating unstable chromium. Before the chromium decays, it can fuse with another helium nucleus, creating unstable iron. Before the iron decays, it can fuse with another helium nucleus, creating unstable nickel-56. Any further fusion of nickel-56 consumes energy instead of producing energy, so after the production of nickel-56, the star does not produce the energy necessary to keep the core from collapsing. Eventually, the nickel-56 decays to unstable cobalt-56 which, in turn decays to stable iron-56 When the core of the star collapses, it creates a Supernova. Supernovas also create additional forms of stable iron via the r-process.

Occurrence

Planetary occurrence

Iron meteorites of similar composition of Earth's inner and outer core

Iron is the sixth most abundant element in the Universe, formed as the final step of nucleosynthesis, by silicon fusing in massive stars. Metallic iron is rarely found on the surface of the earth because it tends to oxidize, but its oxides are pervasive and represent the primary ores. While it makes up about 5% of the Earth's crust, both the Earth's inner and outer core are believed to consist largely of an iron-nickel alloy constituting 35% of the mass of the Earth as a whole. Iron is consequently the most abundant element on Earth, but only the fourth most abundant element in the Earth's crust. Most of the iron in the crust is found combined with oxygen as iron oxide minerals such as hematite and magnetite. Large deposits of iron are found in banded iron formations. These geological formations are a type of rock consisting of repeated thin layers of iron oxides, either magnetite (Fe_3O_4) or hematite (Fe_2O_3), alternating with bands of iron-poor shale and chert. The banded iron formations are common in the time between 3,700 million years ago and 1,800 million years ago

About 1 in 20 meteorites consist of the unique iron-nickel minerals taenite (35–80% iron) and kamacite (90–95% iron). Although rare, iron meteorites are the main form of natural metallic iron on the Earth's surface. It was proven by Mössbauer spectroscopy that the red color of the surface of Mars is derived from an iron oxide-rich regolith.

Chemistry and compounds

Oxidation state	Representative compound
−2	Disodium tetracarbonylferrate (Collman's reagent)
−1	
0	Iron pentacarbonyl
1	Cyclopentadienyliron dicarbonyl dimer ("Fp_2")
2	Ferrous sulfate, ferrocene
3	Ferric chloride, ferrocenium tetrafluoroborate
4	Barium ferrate(IV)
5	
6	Potassium ferrate

Iron forms compounds mainly in the +2 and +3 oxidation states. Traditionally, iron(II) compounds are called ferrous, and iron(III) compounds ferric. Iron also occurs in higher oxidation states, an example being the purple potassium ferrate (K_2FeO_4) which contains iron in its +6 oxidation state. Iron(IV) is a common intermediate in many in biochemical oxidation reactions. Numerous organometallic compounds contain formal oxidation states of +1, 0, −1, or even −2. The oxidation states and other bonding properties are often assessed using the technique of Mössbauer spectroscopy. There are also many mixed valence compounds that contain both iron(II) and iron(III) centers, such as magnetite and Prussian blue ($Fe_4(Fe[CN]_6)_3$). The latter is used as the traditional "blue" in blueprints.

Hydrated iron(III) chloride, also known as ferric chloride

The iron compounds produced on the largest scale in industry are iron(II) sulfate ($FeSO_4 \cdot 7H_2O$) and iron(III) chloride ($FeCl_3$). The former is one of the most readily available sources of iron(II), but is less stable to aerial oxidation than Mohr's salt ($(NH_4)_2Fe(SO_4)_2 \cdot 6H_2O$). Iron(II) compounds tend to be oxidized to iron(III) compounds in the air.

Unlike many other metals, iron does not form amalgams with mercury. As a result, mercury is traded in standardized 76 pound flasks (34 kg) made of iron.

Binary compounds

Iron reacts with oxygen in the air to form various oxide and hydroxide compounds; the most common are iron(II,III) oxide (Fe_3O_4), and iron(III) oxide (Fe_2O_3). Iron(II) oxide also exists, though it is unstable at room temperature. These oxides are the principal ores for the production of iron. They are also used in the production of ferrites, useful magnetic storage media in computers, and pigments. The best known sulfide is iron pyrite (FeS_2), also known as fool's gold owing to its golden luster.

The binary ferrous and ferric halides are well known, with the exception of ferric iodide. The ferrous halides typically arise from treating iron metal with the corresponding binary halogen acid to give the corresponding hydrated salts.

$$Fe + 2\ HX \rightarrow FeX_2 + H_2$$

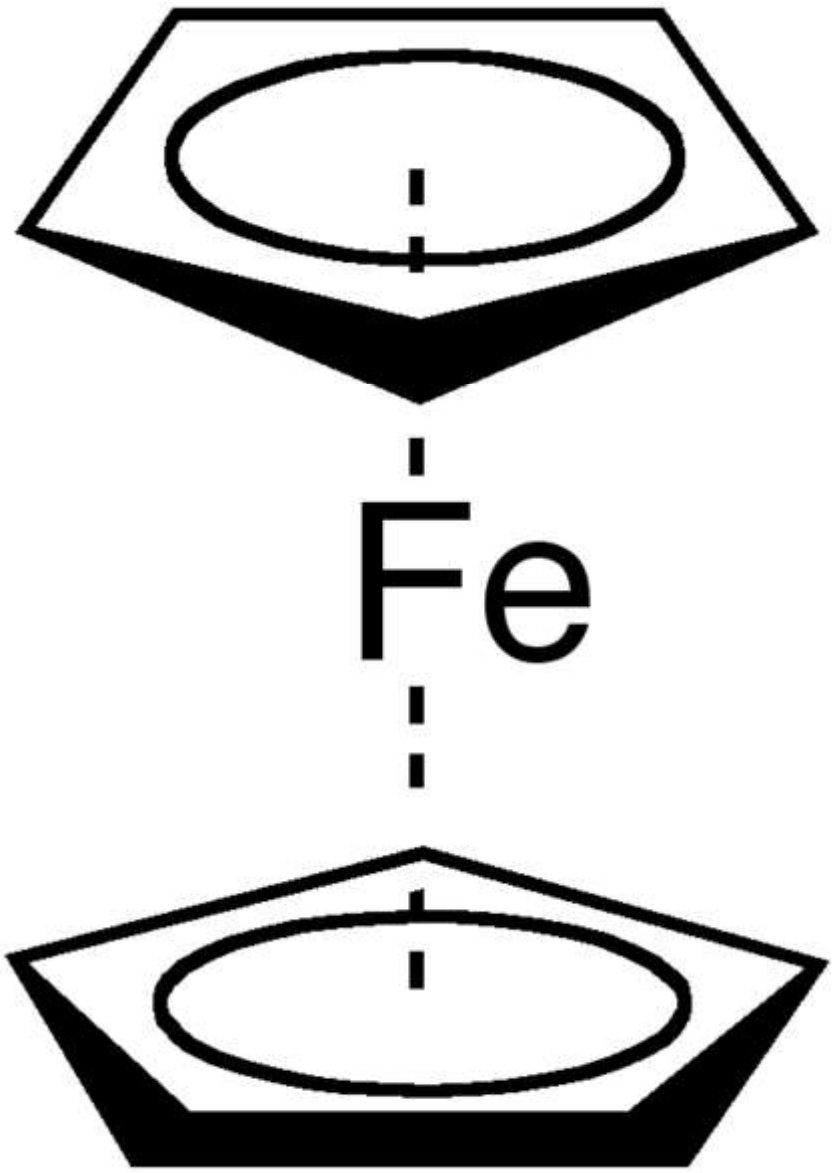
Iron reacts with fluorine, chlorine, and bromine to give the corresponding ferric halides, ferric chloride being the most common:

$$2\ Fe + 3\ X_2 \rightarrow 2\ FeX_3\ (X = F, Cl, Br)$$

Coordination and organometallic compounds

Prussian blue

Several cyanide complexes are known. The most famous example is Prussian blue, ($Fe_4(Fe[CN]_6)_3$). Potassium ferricyanide and potassium ferrocyanide are also known; the formation of Prussian blue upon reaction with iron(II) and iron(III) respectively forms the basis of a "wet" chemical test. Prussian blue is also used as an antidote for thallium and radioactive caesium poisoning. Prussian blue can be used in laundry bluing to correct the yellowish tint left by ferrous salts in water.



Ferrocene

Several carbonyl compounds of iron are known. The premier iron(0) compound is iron pentacarbonyl, $Fe(CO)_5$, which is used to produce carbonyl iron powder, a highly reactive form of metallic iron. Thermolysis of iron pentacarbonyl gives the trinuclear cluster, triiron dodecacarbonyl. Collman's reagent, disodium tetracarbonylferrate, is a useful reagent for organic chemistry; it contains iron in the −2 oxidation state. Cyclopentadienyliron dicarbonyl dimer contains iron in the rare +1 oxidation state.

Ferrocene is an extremely stable complex. The first sandwich compound, it contains an iron(II) center with two cyclopentadienyl ligands bonded through all ten carbon atoms. This arrangement was a shocking novelty when it was first discovered, but the discovery of ferrocene has led to a new branch of organometallic chemistry. Ferrocene itself can be

used as the backbone of a ligand, e.g. dppf. Ferrocene can itself be oxidized to the ferrocenium cation (Fc^+); the ferrocene/ferrocenium couple is often used as a reference in electrochemistry.

Industrial production

The production of iron or steel is a process containing two main stages, unless the desired product is cast iron. The first stage is to produce pig iron in a blast furnace. Alternatively, it may be directly reduced. The second is to make wrought iron or steel from pig iron by a further process.

For a few limited purposes like electromagnet cores, pure iron is produced by electrolysis of a ferrous sulfate solution

Blast furnace

Ninety percent of all mining of metallic ores is for the extraction of iron. Industrially, iron production involves iron ores, principally hematite (nominally Fe_2O_3) and magnetite (Fe_3O_4) in a carbothermic reaction (reduction with carbon) in a blast furnace at temperatures of about 2000 °C. In a blast furnace, iron ore, carbon in the form of coke, and a *flux* such as limestone (which is used to remove silicon dioxide impurities in the ore which would otherwise clog the furnace with solid material) are fed into the top of the furnace, while a massive blast of heated air, about 4 tons per ton of iron, is forced into the furnace at the bottom.

In the furnace, the coke reacts with oxygen in the air blast to produce carbon monoxide:

$$2\ C + O_2 \rightarrow 2\ CO$$

The carbon monoxide reduces the iron ore (in the chemical equation below, hematite) to molten iron, becoming carbon dioxide in the process:

$$Fe_2O_3 + 3\ CO \rightarrow 2\ Fe + 3\ CO_2$$

Some iron in the high-temperature lower region of the furnace reacts directly with the coke:

$$2\ Fe_2O_3 + 3\ C \rightarrow 4\ Fe + 3\ CO_2$$

The flux is present to melt impurities in the ore, principally silicon dioxide sand and other silicates. Common fluxes include limestone (principally calcium carbonate) and dolomite (calcium-magnesium carbonate). Other fluxes may be used depending on the impurities that need to be removed from the ore. In the heat of the furnace the limestone flux decomposes to calcium oxide (also known as quicklime):

$$CaCO_3 \rightarrow CaO + CO_2$$

Then calcium oxide combines with silicon dioxide to form a liquid *slag*.

$$CaO + SiO_2 \rightarrow CaSiO_3$$

The slag melts in the heat of the furnace. In the bottom of the furnace, the molten slag floats on top of the denser molten iron, and apertures in the side of the furnace are opened to run off the iron and the slag separately. The iron, once cooled, is called pig iron, while the slag can be used as a material in road construction or to improve mineral-poor soils for agriculture

This heap of iron ore pellets will be used in steel production

In 2005, approximately 1,544 million metric tons of iron ore were produced worldwide. According to the British Geological Survey, China was the top producer of iron ore with at least one quarter world share, followed by Brazil, Australia and India.

Direct iron reduction

Since coke is becoming more regulated due to environmental concerns, alternative methods of processing iron have been developed. One of them is known as direct iron reduction. It reduces iron ore to a powder substance called sponge iron, which is suitable for steelmaking. There are two main reactions that go on in the direct reduction process:

Natural gas is partially oxidized (with heat and a catalyst):

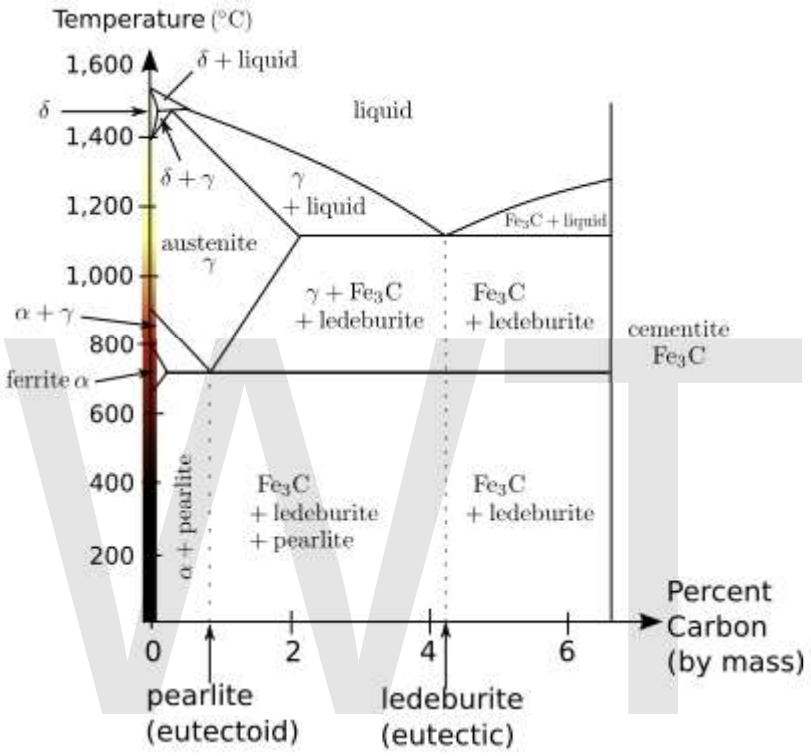
$$2\ CH_4 + O_2 \rightarrow 2\ CO + 4\ H_2$$

These gases are then treated with iron ore in a furnace, producing solid sponge iron:

$$Fe_2O_3 + CO + 2\ H_2 \rightarrow 2\ Fe + CO_2 + 2\ H_2O$$

Silica is removed by adding a flux, i.e. limestone, later.

Further processes



Iron-carbon phase diagram, various stable solid solution forms

Pig iron is not pure iron, but has 4–5% carbon dissolved in it with small amounts of other impurities like sulfur, magnesium, phosphorus and manganese. As the carbon is the major impurity, the iron (pig iron) becomes brittle and hard. This form of iron, also known as cast iron, is used to cast articles in foundries such as stoves, pipes, radiators, lamp-posts and rails.

Alternatively pig iron may be made into steel (with up to about 2% carbon) or wrought iron (commercially pure iron). Various processes have been used for this, including finery forges, puddling furnaces, Bessemer converters, open hearth furnaces, basic oxygen furnaces, and electric arc furnaces. In all cases, the objective is to oxidize some or all of the carbon, together with other impurities. On the other hand, other metals may be added to make alloy steels.

The hardness of the steel depends upon its carbon content: the higher the percentage of carbon, the greater the hardness and the lesser the malleability. The properties of the steel can also be changed by several methods.

Annealing involves the heating of a piece of steel to 700–800 °C for several hours and then gradual cooling. It makes the steel softer and more workable.

Steel may be hardened by cold working. The metal is bent or hammered into its final shape at a relatively cool temperature. Cold forging is the stamping of a piece of steel into shape by a heavy press. Wrenches are commonly made by cold forging. Cold rolling, which involves making a thinner but harder sheet, and cold drawing, which makes a thinner but stronger wire, are two other methods of cold working. To harden the steel, it is heated to red hot and then cooled by quenching it in the water. It becomes harder and more brittle. If it is too hardened, it is then heated to a required temperature and allowed to cool. The steel thus formed is less brittle.

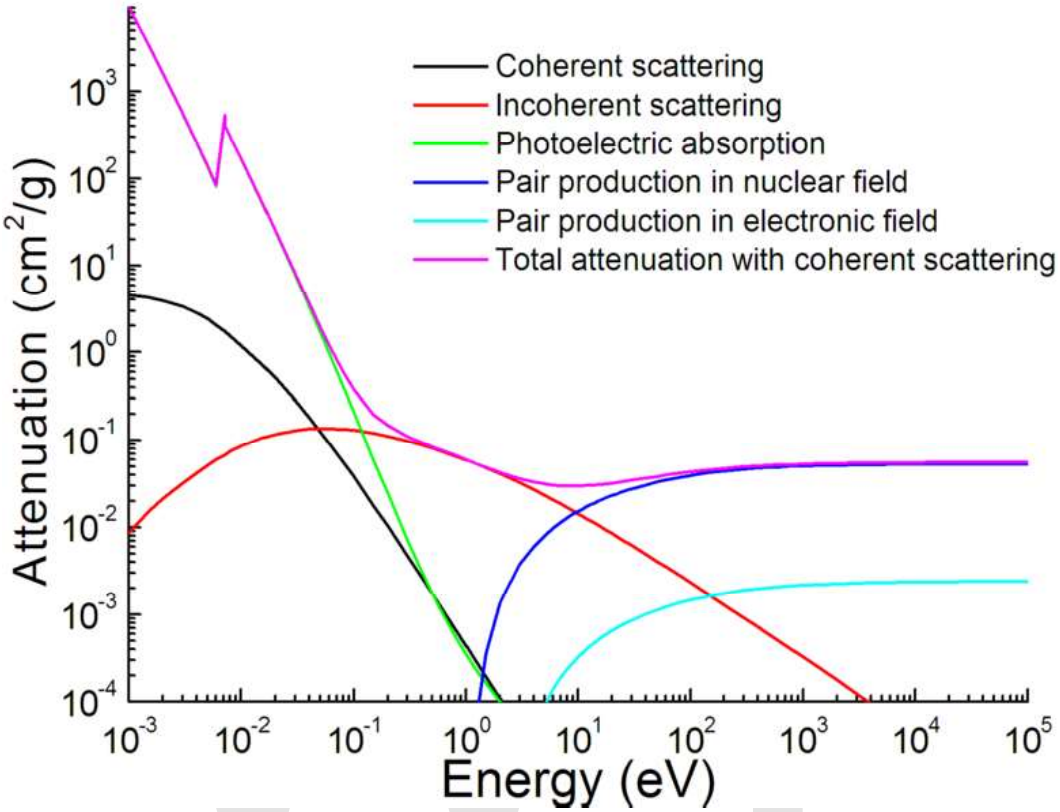
Heat treatment is another way to harden steel. The steel is heated red hot, then cooled quickly. The iron carbide molecules are decomposed by the heat, but do not have time to reform. Since the free carbon atoms are stuck, it makes the steel much harder and stronger than before.

Sometimes both toughness and hardness are desired. A process called case hardening may be used. Steel is heated to about 900 °C in a bed of charcoal and/or nitrogen. They diffuse into the steel, making the surface very hard. The surface cools quickly, but the inside cools slowly, making an extremely hard surface and a durable, resistant inner layer.

Iron may be passivated by dipping it into a concentrated nitric acid solution. This forms a protective layer of oxide on the metal, protecting it from further corrosion. When the metal is jarred, however, the layer is broken, allowing the metal to corrode again.

Applications

Metallurgical



Photon mass attenuation coefficient for iron

Iron is the most widely used of all the metals, accounting for 95% of worldwide metal production. Its low cost and high strength make it indispensable in engineering applications such as the construction of machinery and machine tools, automobiles, the hulls of large ships, and structural components for buildings. Since pure iron is quite soft, it is most commonly used in the form of steel.

Commercially available iron is classified based on purity and the abundance of additives. Pig iron has 3.5–4.5% carbon and contains varying amounts of contaminants such as sulfur, silicon and phosphorus. Pig iron is not a saleable product, but rather an intermediate step in the production of cast iron and steel from iron ore. Cast iron contains 2–4% carbon, 1–6% silicon, and small amounts of manganese. Contaminants present in pig iron that negatively affect material properties, such as sulfur and phosphorus, have been reduced to an acceptable level. It has a melting point in the range of 1420–1470 K, which is lower than either of its two main components, and makes it the first product to be melted when carbon and iron are heated together. Its mechanical properties vary greatly, dependent upon the form carbon takes in the alloy.

"White" cast irons contain their carbon in the form of cementite, or iron carbide. This hard, brittle compound dominates the mechanical properties of white cast irons, rendering them hard, but unresistant to shock. The broken surface of a white cast iron is full of fine facets of the broken carbide, a very pale, silvery, shiny material, hence the appellation.

In gray iron the carbon exists free as fine flakes of graphite, and also renders the material brittle due to the stress-raising nature of the sharp edged flakes of graphite. A newer variant of gray iron, referred to as ductile iron is specially treated with trace amounts of magnesium to alter the shape of graphite to spheroids, or nodules, vastly increasing the toughness and strength of the material.

Wrought iron contains less than 0.25% carbon. It is a tough, malleable product, but not as fusible as pig iron. If honed to an edge, it loses it quickly. Wrought iron is characterized by the presence of fine fibers of slag entrapped in the metal. Wrought iron is more corrosion resistant than steel. It has been almost completely replaced by mild steel for traditional "wrought iron" products and blacksmithing.

Mild steel corrodes more readily that wrought iron, but is cheaper and more widely available. Carbon steel contains 2.0% carbon or less, with small amounts of manganese, sulfur, phosphorus, and silicon. Alloy steels contain varying amounts of carbon as well as other metals, such as chromium, vanadium, molybdenum, nickel, tungsten, etc. Their alloy content raises their cost, and so they are usually only employed for specialist uses. One common alloy steel, though, is stainless steel. Recent developments in ferrous metallurgy have produced a growing range of microalloyed steels, also termed 'HSLA' or high-strength, low alloy steels, containing tiny additions to produce high strengths and often spectacular toughness at minimal cost.

Apart from traditional applications, iron is also used for protection from ionizing radiation. Although it is lighter than another traditional protection material, lead, it is much stronger mechanically. The attenuation of radiation as a function of energy is shown in the graph.

The main disadvantage of iron and steel is that pure iron, and most of its alloys, suffer badly from rust if not protected in some way. Painting, galvanization, passivation, plastic coating and bluing are all used to protect iron from rust by excluding water and oxygen or by cathodic protection.

Of compounds

Although its metallurgical role is dominant in terms of amounts, iron compounds are pervasive in industry as well being used in many niche uses. Iron catalysts are traditionally used in the Haber-Bosch Process for the production of ammonia and the Fischer-Tropsch process for conversion of carbon monoxide to hydrocarbons for fuels and lubricants. Powdered iron in an acidic solvent was used in the Bechamp reduction the reduction of nitrobenzene to aniline.

Iron(III) chloride finds use in water purification and sewage treatment, in the dyeing of cloth, as a coloring agent in paints, as an additive in animal feed, and as an etchant for copper in the manufacture of printed circuit boards. It can also be dissolved in alcohol to form tincture of iron. The other halides tend to be limited to laboratory uses.

Iron(II) sulfate is used as a precursor to other iron compounds. It is also used to reduce chromate in cement. It is used to fortify foods and treat iron deficiency anemia. These are its main uses. Iron(III) sulfate is used in settling minute sewage particles in tank water. Iron(II) chloride is used as a reducing flocculating agent, in the formation of iron complexes and magnetic iron oxides, and as a reducing agent in organic synthesis.

Uptake and storage

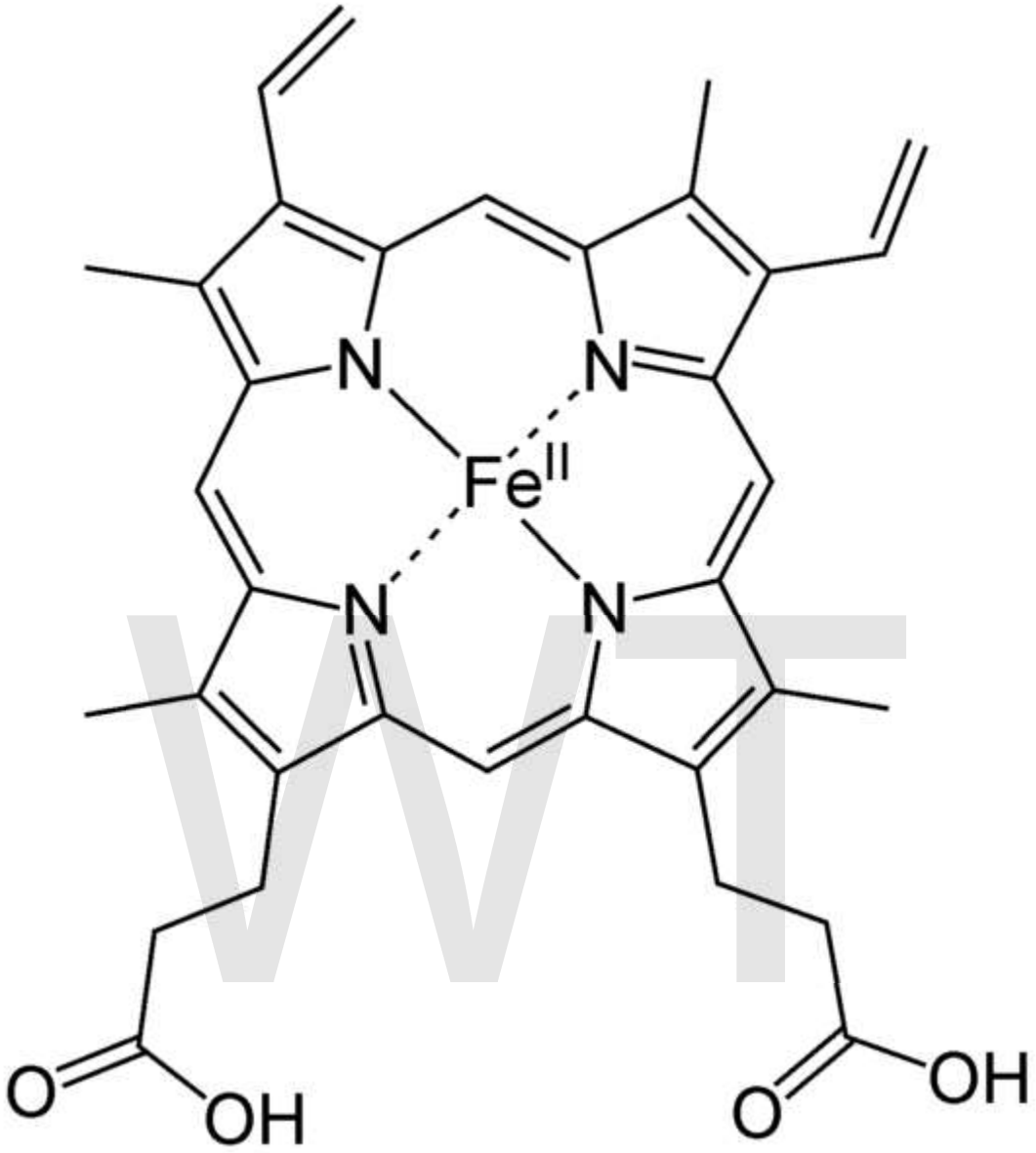
In cells, iron storage is carefully regulated; "free" iron ions do not exist as such. A major component of this regulation is the protein transferrin, which binds iron ions absorbed from the duodenum and carries it in the blood to cells. In animals, plants, and fungi, iron is often the metal ion incorporated into the heme complex. Heme is an essential component of cytochrome proteins, which mediate redox reactions, and of oxygen carrier proteins such as hemoglobin, myoglobin, and leghemoglobin. Inorganic iron also contributes to redox reactions in the iron-sulfur clusters of many enzymes, such as nitrogenase (involved in the synthesis of ammonia from nitrogen and hydrogen) and hydrogenase. Non-heme iron proteins include the enzymes methane monooxygenase (oxidizes methane to methanol), ribonucleotide reductase (reduces ribose to deoxyribose; DNA biosynthesis), hemerythrins (oxygen transport and fixation in Marine invertebrates) and purple acid phosphatase (hydrolysis of phosphate esters).

Iron distribution is heavily regulated in mammals, partly because iron ions have a high potential for biological toxicity.

Iron acquisition poses a problem for aerobic organisms because ferric iron is poorly soluble near neutral pH. Thus, bacteria have evolved high-affinity sequestering agents called siderophores.

Biological role

Iron is abundant in biology. Iron-proteins are found in all living organisms, ranging from the evolutionarily primitive archaea to humans. The color of blood is due to the hemoglobin, an iron-containing protein. As illustrated by hemoglobin, iron often is bound to cofactors, e.g. in hemes. The iron-sulfur clusters are pervasive and include nitrogenase, the enzymes responsible for biological nitrogen fixation. Influential theories of evolution have invoked a role for iron sulfides, iron-sulfur world theory.



Structure of Heme b, in the protein additional ligand(s) would be attached to Fe

Iron is a necessary trace element found in nearly all living organisms. Iron-containing enzymes and proteins, often containing heme prosthetic groups, participate in many biological oxidations and in transport. Examples of proteins found in higher organisms include hemoglobin, cytochrome, and catalase.

Bioinorganic compounds

The most famous bioinorganic compounds of iron are heme proteins: hemoglobin, myoglobin, and cytochrome P450. These compounds can transport gases, build enzymes and be used in transferring electrons. Metalloproteins are a group of proteins with metal

ion cofactors. Some examples of iron metalloproteins are ferritin and rubredoxin. Many enzymes vital to life contain iron, such as catalase, lipoxygenases,and IRE-BP.

Health and diet

Iron is pervasive, but particularly rich sources of dietary iron include red meat, lentils, beans, poultry, fish, leaf vegetables, tofu, chickpeas, black-eyed peas, blackstrap molasses, fortified bread, and fortified breakfast cereals. Iron in low amounts is found in molasses, teff and farina. Iron in meat (heme iron) is more easily absorbed than iron in vegetables. Although most studies suggest that heme/hemoglobin from red meat has effects which may increase the likelihood of colorectal cancer, there is still some controversy, and even a few studies suggesting that there is not enough evidence to support such claims.

Iron provided by dietary supplements is often found as iron(II) fumarate, although iron sulfate is cheaper and is absorbed equally well. Elemental iron, or reduced iron, despite being absorbed at only one third to two thirds the efficiency (relative to iron sulfate), is often added to foods such as breakfast cereals or enriched wheat flour. Iron is most available to the body when chelated to amino acids and is also available for use as a common iron supplement. Often the amino acid chosen for this purpose is the cheapest and most common amino acid, glycine, leading to "iron glycinate" supplements. The Recommended Dietary Allowance (RDA) for iron varies considerably based on age, gender, and source of dietary iron (heme-based iron has higher bioavailability). Infants may require iron supplements if they are bottle-fed cow's milk. Blood donors and pregnant women are at special risk of low iron levels and are often advised to supplement their iron intake.

Regulation of uptake

Iron uptake is tightly regulated by the human body, which has no regulated physiological means of excreting iron. Only small amounts of iron are lost daily due to mucosal and skin epithelial cell sloughing, so control of iron levels is mostly by regulating uptake. Regulation of iron uptake is impaired in some people as a result of a genetic defect that maps to the HLA-H gene region on chromosome 6. In these people, excessive iron intake can result in iron overload disorders, such as hemochromatosis. Many people have a genetic susceptibility to iron overload without realizing it or being aware of a family history of the problem. For this reason, it is advised that people do not take iron supplements unless they suffer from iron deficiency and have consulted a doctor. Hemochromatosis is estimated to cause disease in between 0.3 and 0.8% of Caucasians.

MRI finds that iron accumulates in the hippocampus of the brains of those with Alzheimer's disease and in the substantia nigra of those with Parkinson disease.

Permeable reactive barriers

Zero-valent iron is the main reactive material for permeable reactive barriers.

Precautions

Large amounts of ingested iron can cause excessive levels of iron in the blood. High blood levels of free ferrous iron react with peroxides to produce free radicals, which are highly reactive and can damage DNA, proteins, lipids, and other cellular components. Thus, iron toxicity occurs when there is free iron in the cell, which generally occurs when iron levels exceed the capacity of transferrin to bind the iron. Damage to the cells of the gastrointestinal tract can also prevent them from regulating iron absorption leading to further increases in blood levels. Iron typically damages cells in the heart, liver and elsewhere, which can cause significant adverse effects, including coma, metabolic acidosis, shock, liver failure, coagulopathy, adult respiratory distress syndrome, long-term organ damage, and even death. Humans experience iron toxicity above 20 milligrams of iron for every kilogram of mass, and 60 milligrams per kilogram is considered a lethal dose. Overconsumption of iron, often the result of children eating large quantities of ferrous sulfate tablets intended for adult consumption, is one of the most common toxicological causes of death in children under six. The Dietary Reference Intake (DRI) lists the Tolerable Upper Intake Level (UL) for adults as 45 mg/day. For children under fourteen years old the UL is 40 mg/day.

The medical management of iron toxicity is complicated, and can include use of a specific chelating agent called deferoxamine to bind and expel excess iron from the body.

Chapter- 4

Iodine

Appearance
Lustrous metallic gray, violet as a gas

General properties	
Name, symbol, number	iodine, I, 53
Element category	halogen
Group, period, block	17, 5, p
Standard atomic weight	126.90447g·mol^{-1}
Electron configuration	[Kr] 4d^{10} 5s^{2} 5p^{5}
Electrons per shell	2, 8, 18, 18, 7 (Image)

Physical properties	
Phase	solid
Density (near r.t.)	4.933 g·cm^{-3}
Melting point	386.85 K113.7 ° ,C236.66 ° ,F
Boiling point	457.4 K184.3 ° ,C363.7 ° ,F
Triple point	386.65 K (113°C), 12.1 kPa
Critical point	819 K, 11.7 MPa
Heat of fusion	(I_2) 15.52 kJ·mol^{-1}
Heat of vaporization	(I_2) 41.57 kJ·mol^{-1}
Specific heat capacity	(25 °C) (I_2) 54.44 J·mol^{-1}·K^{-1}

Vapor pressure (rhombic)

P (Pa)	1	10	100	1 k	10 k	100 k
at T (K)	260	282	309	342	381	457

Atomic properties	
Oxidation states	**7**, 5, 3, 1, -1 (strongly acidic oxide)
Electronegativity	2.66 (Pauling scale)

Ionization energies	1st: 1008.4 kJ·mol^{-1}
	2nd: 1845.9 kJ·mol^{-1}
	3rd: 3180 kJ·mol^{-1}
Atomic radius	140 pm
Covalent radius	139±3 pm
Van der Waals radius	198 pm
Miscellanea	
Crystal structure	orthorhombic
Magnetic ordering	diamagnetic
Electrical resistivity	(0 °C) 1.3×10^{7}Ω·m
Thermal conductivity	(300 K) 0.449 W·m^{-1}·K^{-1}
Bulk modulus	7.7 GPa
CAS registry number	7553-56-2

Most stable isotopes

iso	NA	half-life	DM	DE (MeV)	DP
^{123}I	syn	13 h	ε, γ	0.16	^{123}Te
^{127}I	100%	^{127}I is stable with 74 neutrons			
^{129}I	trace	15.7×10^{6} y	β$^-$	0.194	^{129}Xe
^{131}I	syn	8.02070 d	β$^-$, γ	0.971	^{131}Xe

Iodine is a chemical element that has the symbol **I** and the atomic number 53.

Iodine and its compounds are primarily used in nutrition, the production of acetic acid and polymers. Iodine's relatively high atomic number, low toxicity, and ease of attachment to organic compounds have made it a part of many X-ray contrast materials in modern medicine.

Like the other halogens, iodine occurs mainly as a diatomic molecule I_2, not the atom. In nature, iodine is a relatively rare element, ranking 47th in abundance. It is the heaviest essential element utilized widely by life in biological functions (only tungsten, employed in enzymes by a few species of bacteria, is heavier). Its rarity in many soils has led to many deficiency problems in land animals and inland human populations, with iodine deficiency affecting about two billion people and being the leading preventable cause of mental retardation. As a component of thyroid hormones, iodine is required by higher animals. Radioisotopes of iodine are concentrated in the thyroid gland. This property of thyroid-concentration, along with its mode of beta decay, makes iodine-131 one of the most carcinogenic nuclear fission products.

Characteristics

Iodine under standard conditions is a bluish-black solid. It can be seen apparently sublimating at standard temperatures into a violet-pink gas that has an irritating odor. This halogen forms compounds with many elements, but is less reactive than the other members of its Group VII (halogens) and has some metallic light reflectance.

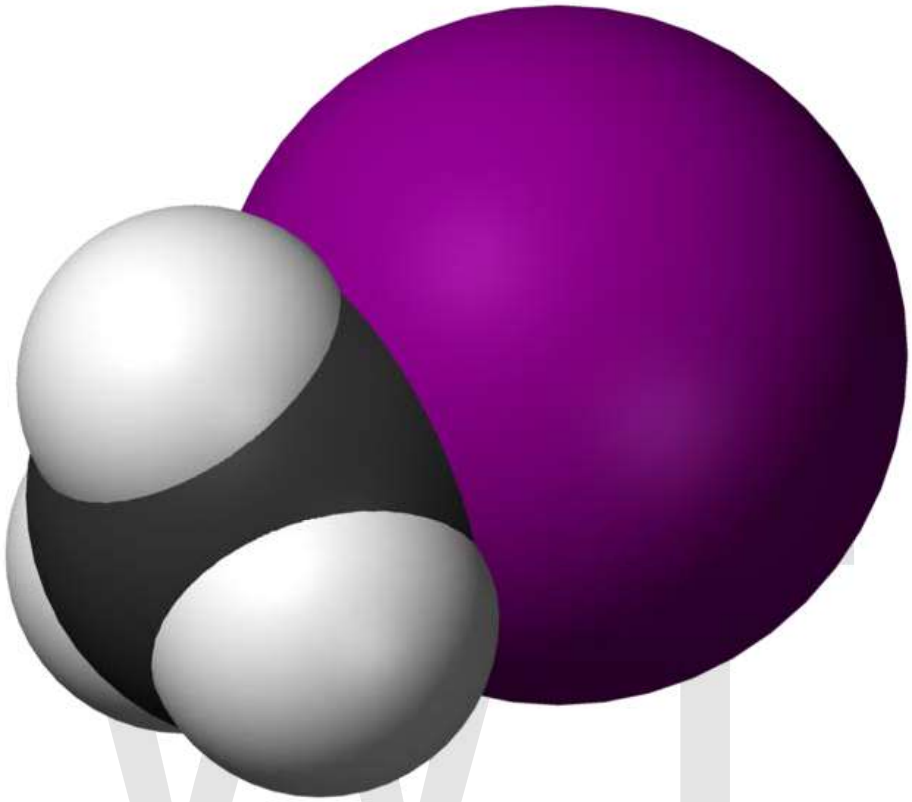
In the gas phase, iodine shows its violet color

Elemental iodine dissolves easily in most organic solvents such as hexane or chloroform due to its lack of polarity, but is only slightly soluble in water. However, the solubility of elemental iodine in water can be increased by the addition of potassium iodide. The molecular iodine reacts reversibly with the negative ion, generating the triiodide anion I_3^- in equilibrium, which is soluble in water. This is also the formulation of some types of medicinal (antiseptic) iodine, although tincture of iodine classically dissolves the element in aqueous ethanol.

The colour of solutions of elemental iodine change depends on the polarity of the solvent. In non-polar solvents like hexane, solution are violet; in moderately polar dichloromethane, the solution is dark crimson, and, in strongly polar solvents such as acetone or ethanol, it appears orange or brown. This effect is due to the formation of adducts.

Iodine melts at the relatively low temperature of 113.7 °C, although the liquid is often obscured by a dense violet vapor of gaseous iodine.

Occurrence

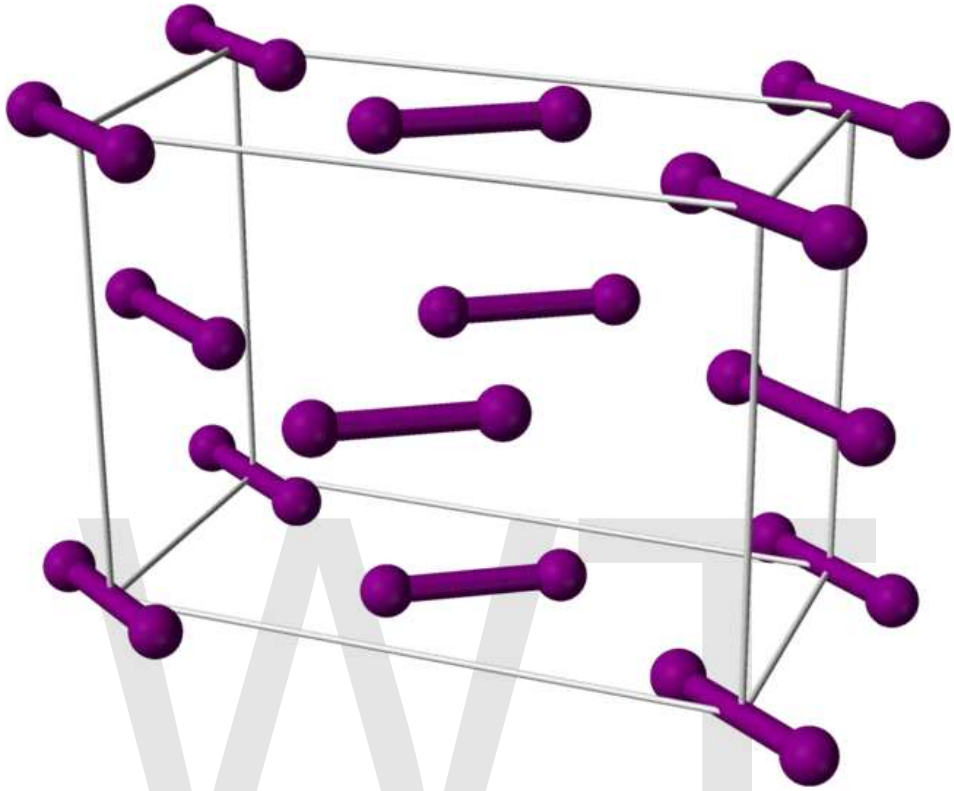


Iodomethane

Iodine is rare in the solar system and Earth's crust (47th in abundance); however, iodide salts are often very soluble in water. Iodine occurs in slightly greater concentrations in seawater than in rocks, 0.05 vs 0.04 ppm. Minerals containing iodine include caliche, found in Chile. A type of seaweed, kelp, tends to be high in iodine as well, with from 0.03 – 0.45 dry weight percent. Aside from tungsten, iodine is the heaviest element to be essential in living organisms, and iodine is the heaviest element thought to be needed by higher animals. About 19,000 tons are produced annually from natural sources.

Organoiodine compounds are produced by marine life forms, the most notable being iodomethane (commonly called methyl iodide). The total iodomethane that is produced by the marine environment, by microbial activity in rice paddies and by the burning of biological material is estimated to be 214 kilotonnes/year. The volatile iodomethane is broken up in the atmosphere as part of a global iodine cycle.

Structure and bonding



Structure of solid iodine

Crystalline iodine

Iodine normally exists as a diatomic molecule with a I-I bond length of 270 pm, one of the longest single bonds known. The I_2 molecules tend to interact via van der Waals forces, and this interaction is responsible for the higher melting point compared to more compact halogens, which are also diatomic. The solid crystallizes in the orthorhombic space group Cmca No 64, Pearson symbol oS8, the same as black phosphorus. The I-I bond is relatively weak, with a bond dissociation energy of 36 kcal/mol. In fact, most bonds to iodine tend to be weaker than for the lighter halides. One consequence of this weak bonding is the relatively high tendency of I_2 molecules to dissociate into atomic iodine.

Production

From the several places in which iodine occurs in nature, only two are used as source for iodine: the caliche, found in Chile, and the iodine containing brines of gas and oil fields, especially in Japan and the United States. The caliche, found in Chile, contains sodium nitrate, which is the main product of the mining activities and small amounts of sodium iodate and sodium iodide. During leaching and production of pure sodium nitrate, the sodium iodate and iodide are extracted. The high concentration of iodine in the caliche and the extensive mining made Chile the largest producer of iodine in 2007.

Most other producers use natural occurring brine for the production of iodine. The Japanese Minami Kanto gas field east of Tokyo and the American Anadarko Basin gas

field in northwest Oklahoma are the two largest sources for iodine from brine. The brine has a temperature of over 60°C due to the depth of the source. The brine is first purified and acidified using sulfuric acid, then the iodide present is oxidized to iodine with chlorine. An iodine solution is produced, but is dilute and must be concentrated. Air is blown into the solution, causing the iodine to evaporate, then it is passed into an absorbing tower containing acid where sulfur dioxide is added to reduce the iodine. The hydrogen iodide (HI) is reacted with chlorine to precipitate the iodine. After filtering and purification the iodine is packed.

$$2\ HI + Cl_2 \rightarrow I_2\uparrow + 2\ HCl$$
$$I_2 + 2\ H_2O + SO_2 \rightarrow 2\ HI + H_2SO_4$$
$$2\ HI + Cl_2 \rightarrow I_2\downarrow + 2\ HCl$$

The production of iodine from seawater via electrolysis is not used due to the sufficient abundance of iodine-rich brine. Another source of iodine was kelp, used in the 18th and 19th centuries, but it is no longer economically viable.

Commercial samples often contain a large amount of impurities; they may be removed by sublimation. The element may also be prepared in an ultra-pure form through the reaction of potassium iodide with copper(II) sulfate, which gives copper(II) iodide initially. That decomposes spontaneously to copper(I) iodide and iodine:

$$Cu^{2+} + 2\ I^- \rightarrow CuI_2$$
$$2\ CuI_2 \rightarrow 2\ CuI + I_2$$

There are also other methods of isolating this element in the laboratory, for example, the method used to isolate other halogens: Oxidation of the iodide in hydrogen iodide (often made *in situ* with an iodide and sulfuric acid) by manganese dioxide.

Isotopes and their applications

There are 37 known (characterized) isotopes of iodine, but only one, ^{127}I, is stable.

The longest-lived radioisotope, ^{129}I, has a half life of 15.7 million years. This is long enough to make it a permanent fixture of the environment on human time scales, but far too short for it to exist as a primordial isotope today. Instead, iodine-129 is an extinct radionuclide, and its presence in the early solar system is inferred from the observation of an excess of its daughter xenon-129. This nuclide is also newly-made by cosmic rays and as a byproduct of human nuclear fission, which it is used to monitor as a very long-lived environmental contaminant.

The next-longest-lived radioisotope, iodine-125, has a half-life of 59 days. It is used as a convenient gamma-emitting tag for proteins in biological assays, and a few nuclear medicine imaging tests where a longer half-life is required. It is also commonly used in brachytherapy implanted capsules, which kill tumors by local short-range gamma radiation (but where the isotope is never released into the body).

Iodine-123 (half-life 13 hours) is the isotope of choice for nuclear medicine imaging of the thyroid gland, which naturally accumulates all iodine isotopes.

Iodine-131 (half-life 8 days) is a beta-emitting isotope, which is a common nuclear fission product. It can be administered to humans safely only in very high doses, which destroy all tissues that accumulate it. Like other radioiodines, it accumulates in the thyroid gland, but unlike the others, in small amounts it is highly carcinogenic there, it seems, due to the high local cell mutation due to damage from beta decay. Because of this tendency of ^{131}I to cause high damage to cells that accumulate it and other cells near them (0.6 to 2 mm away, the range of the beta rays), it is the only iodine radioisotope used as direct therapy to kill tissues such as cancers that take up artificially iodinated molecules (example, the compound MIBG). For the same reason, only this iodine radioisotope is used to treat Grave's disease and thyroid cancers, where the tissues that require destruction naturally take up iodide.

Nonradioactive ordinary potassium iodide (iodine-127), in a number of convenient forms (tablets or solution) may be used to saturate the thyroid gland's ability to take up further iodine, and thus protect against accidental contamination from iodine-131 generated by nuclear fission accidents such as the Chernobyl disaster, as well as from contamination from this isotope in nuclear fallout from nuclear weapons.

Iodine chemistry

Iodine adopts a broad range a variety of oxidation states, commonly ranging from (formally) I^{7+} to I^-, and including the intermediate states of I^{5+}, I^{3+} and I^+. Practically, only the 1- oxidation state is of significance, being the form found in iodide salts and organoiodine compounds.

Solubility

Being a nonpolar molecule, iodine is highly soluble in nonpolar organic solvents, including ethanol (20.5 g/100 ml at 15 °C, 21.43 g/100 ml at 25 °C), diethyl ether (20.6 g/100 ml at 17 °C, 25.20 g/100 ml at 25 °C), chloroform, acetic acid, glycerol, benzene (14.09 g/100 ml at 25 °C), carbon tetrachloride (2.603 g/100 ml at 35 °C), and carbon disulfide (16.47 g/100 ml at 25 °C). Elemental iodine is poorly soluble in water, with one gram dissolving in 3450 ml at 20 °C and 1280 ml at 50 °C. Aqueous and ethanol solutions are brown reflecting the role of these solvents as Lewis bases. Solutions in chloroform, carbon tetrachloride, and carbon disulfide are violet, the color of iodine vapor.

One of the most distinctive properties of iodine is the way that its solubility in water is enhanced by the presence of iodide ions. The dissolution of iodine in aqueous solutions containing iodide (e.g., from hydroiodic acid, potassium iodide, etc.) results from the formation of the I_3^- ion. Dissolved bromides also improve water solubility of iodine.

Redox reactions

In everyday life, iodides are slowly oxidized by atmospheric oxygen in the atmosphere to give free iodine. Evidence for this conversion is the yellow tint of certain aged samples of iodide salts and some organoiodine compounds. The oxidation of iodide to iodine in air is also responsible for the slow loss of iodide content in iodized salt if exposed to air. Some salts use iodate to prevent the loss of iodine.

Iodine is easily oxidized and easily reduced. Most common is the interconversion of I^- and I_2. Molecular iodine can be prepared by oxidizing iodides with chlorine:

$$2\ I^- + Cl_2 \rightarrow I_2 + 2\ Cl^-$$

or with manganese dioxide in acid solution:

$$2\ I^- + 4\ H^+ + MnO_2 \rightarrow I_2 + 2\ H_2O + Mn^{2+}$$

Iodine is reduced to hydroiodic acid by hydrogen sulfide and hydrazine:

$$I_2 + H_2S \rightarrow 2\ HI + 1/8\ S_8$$
$$2\ I_2 + N_2H_4 \rightarrow 4\ HI + N_2$$

When dissolved in fuming sulfuric acid (65% oleum), iodine forms an intense blue solution. The blue color is due to I^{+2} cation, the result of iodine being oxidized by SO_3:

$$2\ I_2 + 2\ SO_3 + H_2SO_4 \rightarrow 2\ I^{+2} + SO_2 + 2\ HSO^-_4$$

The I^{+2} cation is also formed in the oxidation of iodine by SbF_5 or TaF_5. The resulting $I^{+2}Sb_2F^-_{11}$ or $I^{+2}Ta_2F^-_{11}$ can be isolated as deep blue crystals. The solutions of these salts turn red when cooled below −60 °C, due to the formation of the I^{+4}_2 cation:

$$2\ I^{+2} \rightleftharpoons I^{+4}_2$$

Under slightly more alkaline conditions, I^{+4}_2 disproportionates into I^{+3} and an iodine(III) compound. Excess iodine can then react with I^{+3} to form I^{+5} (green) and I^{+15}_3 (black).

Oxides of iodine

The best-known oxides are the anions, IO_3^- and IO_4^-, but several other oxides are known, such as the strong oxidant iodine pentoxide.

By contrast with chlorine, the formation of the hypohalite ion (IO^-) in neutral aqueous solutions of iodine is negligible.

$I_2 + H_2O \rightleftharpoons H^+ + I^- + HIO$ ($K = 2.0\times10^{-13}$) In basic solutions (such as aqueous sodium hydroxide), iodine converts in a two stage reaction to iodide and iodate:

$$I_2 + 2\ OH^- \rightarrow I^- + IO^- + H_2O \quad (K = 30)$$
$$3\ IO^- \rightarrow 2\ I^- + IO_3^- \quad (K = 10^{20})$$

Organic derivatives of hypoiodate (2-Iodoxybenzoic acid, and Dess-Martin periodinane) are used in organic chemistry.

Iodic acid (HIO_3), periodic acid (HIO_4) and their salts are strong oxidizers and are of some use in organic synthesis. Iodine is oxidized to iodate by nitric acid as well as by chlorates:

$$I_2 + 10\ HNO_3 \rightarrow 2\ HIO_3 + 10\ NO_2 + 4\ H_2O$$
$$I_2 + 2\ ClO_3^- \rightarrow 2\ IO_3^- + Cl_2$$

Inorganic iodine compounds

Iodine forms compounds with all the elements except for the noble gases. From the perspective of commercial applications, an important compound is hydroiodic acid, used as a co-catalyst in the Cativa process for the production of acetic acid. Titanium and aluminium iodides are used in the production of butadiene, a precursor to rubber tyres.

Alkali metal salts are common colourless solids that are highly soluble in water. Potassium iodide is a convenient source of the iodide anion; it is easier to handle than sodium iodide because it is not hygroscopic. Both salts are mainly used in the production of iodized salt. Sodium iodide is especially useful in the Finkelstein reaction, because it is soluble in acetone, whereas potassium iodide is less so. In this reaction, an alkyl chloride is converted to an alkyl iodide. This relies on the insolubility of sodium chloride in acetone to drive the reaction:

$$R\text{-}Cl\ (acetone) + NaI\ (acetone) \rightarrow R\text{-}I\ (acetone) + NaCl\ (s)$$

Despite having the lowest electronegativity of the common halogens, iodine reacts violently with some metals, such as aluminium:

$$3\ I_2 + 2\ Al \rightarrow 2\ AlI_3$$

This reaction produces 314 kJ per mole of aluminum, comparable to thermite's 425 kJ. Yet the reaction initiates spontaneously, and if unconfined, causes a cloud of gaseous iodine due to the high temperature.

Interhalogen compounds

Interhalogen compounds are well known; examples include iodine monochloride and trichloride; iodine pentafluoride and heptafluoride.

Organic compounds

Many organoiodine compounds exist; the simplest is iodomethane, approved as a soil fumigant. Iodinated organics are used as synthetic reagents, and also radiocontrast agents.

The thyroid hormones are naturally occurring organoiodine compounds.

Organic synthesis

With phosphorus, iodine is able to replace hydroxyl groups on alcohols with iodide. For example, the synthesis of methyl iodide from methanol, red phosphorus, and iodine. The iodinating reagent is phosphorus triiodide that is formed *in situ*:

$$3\ CH_3OH + PI_3 \rightarrow 3\ CH_3I + H_3PO_3$$

Phosphorous acid is formed as a side-product.

The iodoform test uses an alkaline solution of iodine to react with methyl ketones to give the labile triiodomethide leaving group, forming iodoform, which precipitates.

Iodine is sometimes used to activate magnesium when preparing Grignard reagents; aryl and alkyl iodides both form Grignard reagents. Alkyl iodides such as iodomethane are good alkylating agents. Some drawbacks to use of organoiodine compounds in chemical synthesis are:

- iodine compounds tend to be more expensive than the corresponding bromides and chlorides, in that order
- iodides tend to be much stronger alkylating agents, and so are more toxic (e.g., methyl iodide is very toxic (T+)
- low-molecular-weight iodides tend to have a much higher equivalent weight, compared to other alkylating agents (e.g., methyl iodide versus dimethyl carbonate), due to the atomic mass of iodine.

Analytical chemistry and bioanalysis

Testing a seed for starch with a solution of iodine

Iodine is a common general stain used in thin-layer chromatography. In particular, iodine forms an intense blue complex with the glucose polymers starch and glycogen. Several analytical methods rely on this property:

- Iodometry. The concentration of an oxidant can be determined by adding it to an excess of iodide, to destroy elemental iodine/triiodide as a result of oxidation by the oxidant. A starch indicator is then used as the indicator close to the end-point, in order to increase the visual contrast (dark blue becomes colorless, instead of the yellow of dilute triiodide becoming colorless).
- An Iodine test may be used to test a sample substance for the presence of starch. The Iodine clock reaction is an extension of the techniques in iodometry.
- Iodine solutions are used in counterfeit banknote detection pens; the premise being that counterfeit banknotes made using commercially available paper contain starch.
- Starch-iodide paper are used to test for the presence of oxidants such as peroxides. The oxidants convert iodide to iodine, which shows up as blue. A solution of starch and iodide can perform the same function.

- During colposcopy, Lugol's iodine is applied to the vagina and cervix. Normal vaginal tissue stains brown due to its high glycogen content (a color-reaction similar to that with starch), while abnormal tissue suspicious for cancer does not stain, and thus appears pale compared to the surrounding tissue. Biopsy of suspicious tissue can then be performed. This is called a Schiller's Test.

Clandestine synthetic chemical use

In the United States, the Drug Enforcement Agency (DEA) regards iodine and compounds containing iodine (ionic iodides, iodoform, ethyl iodide, and so on) as reagents useful for the clandestine manufacture of methamphetamine.

Biological role

Iodine is an essential trace element for life, the heaviest element commonly needed by living organisms, and the second-heaviest known to be used by any form of life (only tungsten, a component of a few bacterial enzymes, has a higher atomic number and atomic weight).

Iodine's main role in animal biology is as a constituent of the thyroid hormones *thyroxine* (T4) and *triiodothyronine* (T3). These are made from addition condensation products of the amino acid tyrosine, and are stored prior to release in an iodine-containing protein called thyroglobulin. T4 and T3 contain four and three atoms of iodine per molecule, respectively. The thyroid gland actively absorbs iodide from the blood to make and release these hormones into the blood, actions that are regulated by a second hormone TSH from the pituitary. Thyroid hormones are phylogenetically very old molecules that are synthesized by most multicellular organisms, and that even have some effect on unicellular organisms.

Thyroid hormones play a basic role in biology, acting on gene transcription to regulate the basal metabolic rate. The total deficiency of thyroid hormones can reduce basal metabolic rate up to 50%, while in excessive production of thyroid hormones the basal metabolic rate can be increased by 100%. T4 acts largely as a precursor to T3, which is (with minor exceptions) the biologically active hormone.

Iodine has a nutritional relationship with selenium. A family of selenium-dependent enzymes called deiodinases converts T4 to T3 (the active hormone) by removing an iodine atom from the outer tyrosine ring. These enzymes also convert T4 to reverse T3 (rT3) by removing an inner ring iodine atom, and convert T3 to 3,3'-diiodothyronine (T2) also by removing an inner ring atom. Both of the latter are inactivated hormones that are ready for disposal and have, in essence, no biological effects. A family of non-selenium-dependent enzymes then further deiodinates the products of these reactions.

Iodine accounts for 65% of the molecular weight of T4 and 59% of the T3. Fifteen to 20 mg of iodine is concentrated in thyroid tissue and hormones, but 70% of the body's iodine is distributed in other tissues, including mammary glands, eyes, gastric mucosa,

the cervix, and salivary glands. In the cells of these tissues, iodide enters directly by sodium-iodide symporter (NIS). Its role in mammary tissue is related to fetal and neonatal development, but its role in the other tissues is unknown.

Dietary intake

The daily Dietary Reference Intake recommended by the United States Institute of Medicine is between 110 and 130 μg for infants up to 12 months, 90 μg for children up to eight years, 130 μg for children up to 13 years, 150 μg for adults, 220 μg for pregnant women and 290 μg for lactating mothers. The Tolerable Upper Intake Level (UL) for adults is 1,100 μg/day (1.1 mg/day). The tolerable upper limit was assessed by analyzing the effect of supplementation on thyroid-stimulating hormone.

The thyroid gland needs no more than 70 micrograms /day to synthesize the requisite daily amounts of T4 and T3. The higher recommended daily allowance levels of iodine seem necessary for optimal function of a number of body systems, including lactating breast, gastric mucosa, salivary glands, oral mucosa, thymus, epidermis, choroid plexus, etc. The high iodide-concentration of thymus tissue in particular suggests an anatomical rationale for this role of iodine in the immune system. The trophic, antioxidant and apoptosis-inductor actions and the presumed anti-tumour activity of iodides has been suggested to also be important for prevention of oral and salivary glands diseases.

Natural sources of iodine include sea life, such as kelp and certain seafood, as well as plants grown on iodine-rich soil. Iodized salt is fortified with iodine.

As of 2000, the median intake of iodine from food in the United States was 240 to 300 μg/day for men and 190 to 210 μg/day for women. In Japan, consumption is much higher due to the frequent consumption of seaweed or kombu kelp.

After iodine fortification programs (e.g., iodized salt) have been implemented, some cases of iodine-induced hyperthyroidism have been observed (so called Jod-Basedow disease). The condition seems to occur mainly in people over forty, and the risk appears higher when iodine deficiency is severe and the initial rise in iodine intake is high.

Deficiency

In areas where there is little iodine in the diet, typically remote inland areas and semi-arid equatorial climates where no marine foods are eaten, iodine deficiency gives rise to hypothyroidism, symptoms of which are extreme fatigue, goitre, mental slowing, depression, weight gain, and low basal body temperatures. Iodine deficiency is the leading cause of preventable mental retardation, a result that occurs primarily when babies or small children are rendered hypothyroidic by a lack of the element. The addition of iodine to table salt has largely eliminated this problem in the wealthier nations, but, as of March 2006, iodine deficiency remained a serious public health problem in the developing world. Iodine deficiency is also a problem in certain areas of Europe.

Other possible health effects being investigated as being related to deficiency include:

- **Breast cancer.** The breast strongly and actively concentrates iodine into breast-milk for the benefit of the developing infant, and may develop a goiter-like hyperplasia, sometimes manifesting as fibrocystic breast disease, when iodine level are low. Studies indicate that iodine deficiency, either dietary or pharmacologic, can lead to breast atypia and increased incidence of malignancy in animal models, while iodine treatment can reverse dysplasia. The role of iodide in breast dysplasia and development of breast cancer is an area of active research.

- **Stomach cancer**. Some researchers have found an epidemiologic correlation between iodine deficiency, iodine-deficient goitre and gastric cancer. A decrease of the incidence of death rate from stomach cancer after implementation of the effective iodine-prophylaxis has been reported also.

Precautions and toxicity of elemental iodine

Elemental iodine is an oxidizing irritant and direct contact with skin can cause lesions, so iodine crystals should be handled with care. Solutions with high elemental iodine concentration such as tincture of iodine and Lugol's solution are capable of causing tissue damage if use for cleaning and antisepsis is prolonged.

Elemental iodine (I_2) is poisonous if taken orally in larger amounts; 2–3 grams of it is a lethal dose for an adult human.

Iodine vapor is very irritating to the eye, to mucous membranes, and in the respiratory tract. Concentration of iodine in the air should not exceed 1 mg/m^3 (eight-hour time-weighted average).

When mixed with ammonia and water, elemental iodine forms nitrogen triiodide, which is extremely shock-sensitive and can explode unexpectedly.

Toxicity of iodide ion

Excess iodine has symptoms similar to those of iodine deficiency. Commonly encountered symptoms are abnormal growth of the thyroid gland and disorders in functioning and growth of the organism as a whole. Iodides are similar in toxicity to bromides.

Excess iodine can be more cytotoxic in the presence of selenium deficiency. Iodine supplementation in selenium-deficient populations is, in theory, problematic, partly for this reason.

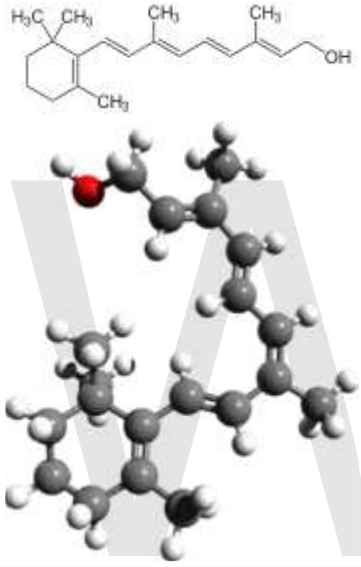
Iodine sensitivity

Some people develop a sensitivity to iodine. Application of tincture of iodine can cause a rash. Some cases of reaction to Povidone-iodine (Betadine) have been documented to be a chemical burn. Eating iodine-containing foods can cause hives. Medical use of iodine (i.e. as a contrast agent, see above) can cause anaphylactic shock in highly iodine-sensitive patients. Some cases of sensitivity to iodine can be formally classified as iodine allergies. Iodine sensitivity is rare but has a considerable effect given the extremely widespread use of iodine-based contrast media.

Chapter- 5

Vitamin A

Vitamin A



Systematic (IUPAC) name	
(2E,4E,6E,8E)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraen-1-ol (Retinol)	
Identifiers	
ChemSpider	393012 ✓
KEGG	D03365
ChEMBL	CHEMBL986 ✓
Chemical data	
Formula	$C_{20}H_{30}O$
Mol. mass	286.4516 g/mol
SMILES	eMolecules & PubChem

Vitamin A is a vitamin that is needed by the retina of the eye in the form of a specific metabolite, the light-absorbing molecule retinal, that is absolutely necessary for both low-light (scotopic vision) and color vision. Vitamin A also functions in a very different role, as an irreversibly oxidized form of retinol known as retinoic acid, which is an important hormone-like growth factor for epithelial and other cells.

In foods of animal origin, the major form of vitamin A is an ester, primarily retinyl palmitate, which is converted to the retinol (chemically an alcohol) in the small intestine. The retinol form functions as a storage form of the vitamin, and can be converted to and from its visually active aldehyde form, retinal. The associated acid (retinoic acid), a metabolite that can be irreversibly synthesized from vitamin A, has only partial vitamin A activity, and does not function in the retina for the visual cycle.

All forms of vitamin A have a beta-ionone ring to which an isoprenoid chain is attached, called a *retinyl group*. Both structural features are essential for vitamin activity. The orange pigment of carrots – beta-carotene – can be represented as two connected retinyl groups, which are used in the body to contribute to vitamin A levels. Alpha-carotene and gamma-carotene also have a single retinyl group, which give them some vitamin activity. None of the other carotenes have vitamin activity. The carotenoid beta-cryptoxanthin possesses an ionone group and has vitamin activity in humans.

Vitamin A can be found in two principal forms in foods:

- retinol, the form of vitamin A absorbed when eating animal food sources, is a yellow, fat-soluble substance. Since the pure alcohol form is unstable, the vitamin is found in tissues in a form of retinyl ester. It is also commercially produced and administered as esters such as retinyl acetate or palmitate.

- The carotenes alpha-carotene, beta-carotene, gamma-carotene; and the xanthophyll beta-cryptoxanthin (all of which contain beta-ionone rings), but no other carotenoids, function as vitamin A in herbivores and omnivore animals, which possess the enzyme required to convert these compounds to retinal. In general, carnivores are poor converters of ionine-containing carotenoids, and pure carnivores such as cats and ferrets lack beta-carotene 15,15'-monooxygenase and cannot convert any carotenoids to retinal (resulting in *none* of the carotenoids being forms of vitamin A for these species).

History

The discovery of vitamin A may have stemmed from research dating back to 1906, indicating that factors other than carbohydrates, proteins, and fats were necessary to keep cattle healthy. By 1917 one of these substances was independently discovered by Elmer McCollum at the University of Wisconsin–Madison, and Lafayette Mendel and Thomas Burr Osborne at Yale University. Since "water-soluble factor B" (vitamin B) had recently been discovered, the researchers chose the name "fat-soluble factor A" (vitamin A). In 1919, Steenbock (University of Wisconsin) proposed a relationship between yellow plant

pigments (beta-carotene) and vitamin A. Vitamin A was first synthesized in 1947 by two Dutch chemists, David Adriaan van Dorp and Jozef Ferdinand Arens.

Equivalencies of retinoids and carotenoids (IU)

As some carotenoids can be converted into vitamin A, attempts have been made to determine how much of them in the diet is equivalent to a particular amount of retinol, so that comparisons can be made of the benefit of different foods. The situation can be confusing because the accepted equivalences have changed. For many years, a system of equivalencies in which an international unit (IU) was equal to 0.3 μg of retinol, 0.6 μg of β-carotene, or 1.2 μg of other provitamin-A carotenoids was used. Later, a unit called retinol equivalent (RE) was introduced. Prior to 2001, one RE corresponded to 1 μg retinol, 2 μg β-carotene dissolved in oil (it is only partly dissolved in most supplement pills, due to very poor solubility in any medium), 6 μg β-carotene in normal food (because it is not absorbed as well as when in oils), and 12 μg of either α-carotene, γ-carotene, or β-cryptoxanthin in food.

Newer research has shown that the absorption of provitamin-A carotenoids is only half as much as previously thought. As a result, in 2001 the US Institute of Medicine recommended a new unit, the retinol activity equivalent (RAE). Each μg RAE corresponds to 1 μg retinol, 2 μg of β-carotene in oil, 12 μg of "dietary" beta-carotene, or 24 μg of the three other dietary provitamin-A carotenoids.

Substance and its chemical environment	**Micrograms of retinol equivalent per microgram of the substance**
retinol	1
beta-carotene, dissolved in oil	1/2
beta-carotene, common dietary	1/12
alpha-carotene, common dietary	1/24
gamma-carotene, common dietary	1/24
beta-cryptoxanthin, common dietary	1/24

Because the conversion of retinol from provitamin carotenoids by the human body is actively regulated by the amount of retinol available to the body, the conversions apply strictly only for vitamin A-deficient humans. The absorption of provitamins depends greatly on the amount of lipids ingested with the provitamin; lipids increase the uptake of the provitamin.

The conclusion that can be drawn from the newer research is that fruits and vegetables are not as useful for obtaining vitamin A as was thought; in other words, the IUs that these foods were reported to contain were worth much less than the same number of IUs of fat-dissolved oils and (to some extent) supplements. This is important for vegetarians, as Night blindness is prevalent in countries where little meat or vitamin A-fortified foods are available.

A sample vegan diet for one day that provides sufficient vitamin A has been published by the Food and Nutrition Board (page 120). On the other hand, reference values for retinol or its equivalents, provided by the National Academy of Sciences, have decreased. The RDA (for men) of 1968 was 5000 IU (1500 μg retinol). In 1974, the RDA was set to 1000 RE (1000 μg retinol), whereas now the Dietary Reference Intake is 900 RAE (900 μg or 3000 IU retinol). This is equivalent to 1800 μg of β-carotene supplement (3000 IU) or 10800 μg of β-carotene in food (18000 IU).

Recommended daily intake

Vitamin A
Dietary Reference Intake:

	RDA	Upper limit
Life stage group	**Adequate intakes (AI*) μg/day**	**μg/day**
Infants		
0–6 months	400*	600
7–12 months	500*	600
Children		
1–3 years	300	600
4–8 years	400	900
Males		
9–13 years	600	1700
14–18 years	900	2800
19 – >70 years	900	3000
Females		
9–13 years	600	1700
14–18 years	700	2800
19 – >70 years	700	3000
Pregnancy		
<19 years	750	2800
19 – >50 years	770	3000
Lactation		
<19 years	1200	2800
19 – >50 years	1300	3000

(Note that the limit refers to synthetic and natural retinol ester forms of vitamin A. Carotene forms from dietary sources are not toxic.)

According to the Institute of Medicine of the National Academies, "RDAs are set to meet the needs of almost all (97 to 98%) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevents being able to specify with confidence the percentage of individuals covered by this intake." To reduce the possible risk of bone fracture and osteoporosis in postmenopausal women, an upper limit intake of 1500 µg RE/d has been recommended.

Sources

Vitamin A is found naturally in many foods:

- liver (beef, pork, chicken, turkey, fish) (6500 µg 722%), including cod liver oil
- carrot (835 µg 93%)
- broccoli leaf (800 µg 89%) – According to USDA database broccoli florets have much less.
- sweet potato (709 µg 79%)
- butter (684 µg 76%)
- kale (681 µg 76%)
- spinach (469 µg 52%)
- pumpkin (400 µg 41%)
- collard greens (333 µg 37%)

- Cheddar cheese (265 μg 29%)
- cantaloupe melon (169 μg 19%)
- egg (140 μg 16%)
- apricot (96 μg 11%)
- papaya (55 μg 6%)
- mango (38 μg 4%)
- pea (38 μg 4%)
- broccoli (31 μg 3%)
- milk (28 μg 3%)

Note: data taken from USDA database bracketed values are retinol activity equivalences (RAEs) and percentage of the adult male RDA, per 100 grams of the foodstuff (average).

Conversion of carotene to retinol varies from person to person and bioavailability of carotene in food varies.

Metabolic functions

Vitamin A plays a role in a variety of functions throughout the body, such as:

- Vision
- Gene transcription
- Immune function
- Embryonic development and reproduction
- Bone metabolism
- Haematopoiesis
- Skin and cellular health
- Antioxidant activity

Vision

The role of vitamin A in the visual cycle is specifically related to the retinal form. Within the eye, 11-*cis*-retinal is bound to rhodopsin (rods) and iodopsin (cones) at conserved lysine residues. As light enters the eye, the 11-*cis*-retinal is isomerized to the all-"trans" form. The all-"trans" retinal dissociates from the opsin in a series of steps called photo-bleaching. This isomerization induces a nervous signal along the optic nerve to the visual center of the brain. After separating from opsin, the all-"trans"-retinal is recycled and converted back to the 11-"cis"-retinal form by a series of enzymatic reactions. In addition, some of the all-"trans" retinal may be converted to all-"trans" retinol form and then transported with an interphotoreceptor retinol-binding protein (IRBP) to the pigment epithelial cells. Further esterification into all-"trans" retinyl esters allow for storage of all-trans-retinol within the pigment epithelial cells to be reused when needed. The final stage is conversion of 11-*cis*-retinal will rebind to opsin to reform rhodopsin in the retina. Rhodopsin is needed to in low light (contrast) as well as for night vision. It is for this reason that a deficiency in vitamin A will inhibit the reformation of rhodopsin and lead to one of the first symptoms, night blindness.

Gene transcription

Vitamin A, in the retinoic acid form, plays an important role in gene transcription. Once retinol has been taken up by a cell, it can be oxidized to retinal (retinaldehyde) by retinol dehydrogenases and then retinaldehyde can be oxidized to retinoic acid by retinaldehyde dehydrogenases. The conversion of retinaldehyde to retinoic acid is an irreversible step, meaning that the production of retinoic acid is tightly regulated, due to its activity as a ligand for nuclear receptors. The physiological form of retinoic acid (all-trans-retinoic acid) regulates gene transcription by binding to nuclear receptors known as retinoic acid receptors (RARs) which are bound to DNA as heterodimers with retinoid "X" receptors (RXRs). RAR and RXR must dimerize before they can bind to the DNA. RAR will form a heterodimer with RXR (RAR-RXR), but it does not readily form a homodimer (RAR-RAR). RXR, on the other hand, may form a homodimer (RXR-RXR) and will form heterodimers with many other nuclear receptors as well, including the thyroid hormone receptor (RXR-TR), the Vitamin D_3 receptor (RXR-VDR), the peroxisome proliferator-activated receptor (RXR-PPAR) and the liver "X" receptor (RXR-LXR). The RAR-RXR heterodimer recognizes retinoic acid response elements (RAREs) on the DNA whereas the RXR-RXR homodimer recognizes retinoid "X" response elements (RXREs) on the DNA; although several RAREs near target genes have been shown to control physiological processes, this has not been demonstrated for RXREs. The heterodimers of RXR with nuclear receptors other than RAR (i.e. TR, VDR, PPAR, LXR) bind to various distinct response elements on the DNA to control processes not regulated by vitamin A. Upon binding of retinoic acid to the RAR component of the RAR-RXR heterodimer, the receptors undergo a conformational change that causes co-repressors to dissociate from the receptors. Coactivators can then bind to the receptor complex, which may help to loosen the chromatin structure from the histones or may interact with the transcriptional machinery. This response can upregulate (or downregulate) the expression of target genes, including Hox genes as well as the genes that encode for the receptors themselves (i.e. RAR-beta in mammals).

Dermatology

Vitamin A, and more specifically, retinoic acid, appears to maintain normal skin health by switching on genes and differentiating keratinocytes (immature skin cells) into mature epidermal cells. Exact mechanisms behind pharmacological retinoid therapy agents in the treatment of dermatological diseases are being researched. For the treatment of acne, the most prescibred retinoid drug is 13-cis retinoic acid (isotretinoin). It reduces the size and secretion of the sebaceous glands. Although it is known that 40 mg of isotretinoin will break down to an equivalent of 10 mg of ATRA — the mechanism of action of the drug (original brand name Accutane) remains unknown and is a matter of some controversy. Isotretinoin reduces bacterial numbers in both the ducts and skin surface. This is thought to be a result of the reduction in sebum, a nutrient source for the bacteria. Isotretinoin reduces inflammation via inhibition of chemotatic responses of monocytes and neutrophils. Isotretinoin also has been shown to initiate remodeling of the sebaceous glands; triggering changes in gene expression that selectively induce apoptosis.

Isotretinoin is a teratogen with a number of potential side-effects. Consequently, its use requires medical supervision.

Retinal/retinol versus retinoic acid

Vitamin A deprived rats can be kept in good general health with supplementation of retinoic acid. This reverses the growth-stunting effects of vitamin A deficiency, as well as early stages of xerophthalmia. However, such rats show infertility (in both male and females) and continued degeneration of the retina, showing that these functions require retinal or retinol, which are intraconvertable but which cannot be recovered from the oxidized retinoic acid. The requirement of retinol to rescue reproduction in vitamin A deficient rats is now known to be due to a requirement for local synthesis of retinoic acid from retinol in testis and embryos.

Deficiency

Vitamin A deficiency is estimated to affect approximately one third of children under the age of five around the world. It is estimated to claim the lives of 670,000 children under five annually. Approximately 250,000–500,000 children in developing countries become blind each year owing to vitamin A deficiency, with the highest prevalence in Southeast Asia and Africa.

Vitamin A deficiency can occur as either a primary or a secondary deficiency. A primary vitamin A deficiency occurs among children and adults who do not consume an adequate intake of provitamin A carotenoids from fruits and vegetables or preformed vitamin A from animal and dairy products. Early weaning from breastmilk can also increase the risk of vitamin A deficiency.

Secondary vitamin A deficiency is associated with chronic malabsorption of lipids, impaired bile production and release, and chronic exposure to oxidants, such as cigarette smoke, and chronic alcoholism. Vitamin A is a fat soluble vitamin and depends on micellar solubilization for dispersion into the small intestine, which results in poor use of vitamin A from low-fat diets. Zinc deficiency can also impair absorption, transport, and metabolism of vitamin A because it is essential for the synthesis of the vitamin A transport proteins and as the cofactor in conversion of retinol to retinal. In malnourished populations, common low intakes of vitamin A and zinc increase the severity of vitamin A deficiency and lead physiological signs and symptoms of deficiency. A study in Burkina Faso showed major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children.

Due to the unique function of retinal as a visual chromophore, one of the earliest and specific manifestations of vitamin A deficiency is impaired vision, particularly in reduced light – night blindness. Persistent deficiency gives rise to a series of changes, the most devastating of which occur in the eyes. Some other ocular changes are referred to as xerophthalmia. First there is dryness of the conjunctiva (xerosis) as the normal lacrimal and mucus-secreting epithelium is replaced by a keratinized epithelium. This is followed

by the build-up of keratin debris in small opaque plaques (Bitot's spots) and, eventually, erosion of the roughened corneal surface with softening and destruction of the cornea (keratomalacia) and total blindness. Other changes include impaired immunity (increased risk of ear infections, urinary tract infections, Meningococcal disease), hyperkeratosis (white lumps at hair follicles), keratosis pilaris and squamous metaplasia of the epithelium lining the upper respiratory passages and urinary bladder to a keratinized epithelium. With relations to dentistry, a deficiency in Vitamin A leads to enamel hypoplasia.

Adequate supply, but not excess vitamin A, is especially important for pregnant and breastfeeding women for normal fetal development. Deficiencies cannot be compensated by postnatal supplementation. Excess vitamin A, which is most common with high dose vitamin supplements, can cause birth defects and therefore should not exceed recommended daily values.

Vitamin A metabolic inhibition as a result of alcohol consumption during pregnancy is the elucidated mechanism for fetal alcohol syndrome and is characterized by teratogenicity closely matching maternal vitamin A deficiency.

Vitamin A supplementation

Global efforts to support national governments in addressing vitamin a deficiency are led by the Global Alliance for Vitamin A (GAVA), which is an informal partnership between A2Z, the Canadian International Development Agency, Helen Keller International, the Micronutrient Initiative, UNICEF, USAID, and the World Bank. Joint GAVA activity is coordinated by the Micronutrient Initiative.

While strategies include intake of vitamin A through a combination of breast feeding and dietary intake, delivery of oral high-dose supplements remain the principal strategy for minimizing deficiency. Studies have shown vitamin A supplementation of children under five who are at risk of deficiency can reduce mortality by 23%. About 75% of the vitamin A required for supplementation activity by developing countries is supplied by the Micronutrient Initiative with support from the Canadian International Development Agency. Food fortification approaches are becoming increasingly feasible but cannot yet ensure coverage levels.

An estimated 1.25 million deaths due to vitamin A deficiency have been averted in 40 countries since 1998. In 2008 it was estimated that an annual investment of US$60 million in vitamin A and zinc supplementation combined would yield benefits of more than US$1 billion per year, with every dollar spent generating benefits of more than US$17. These combined interventions were ranked by the Copenhagen Consensus 2008 as the world’s best development investment.

Toxicity

Since vitamin A is fat-soluble, disposing of any excesses taken in through diet is much harder than with water-soluble B vitamins and vitamin C, and vitamin A toxicity is possible.

In general, acute toxicity occurs at doses of 25,000 IU/kg of body weight, with chronic toxicity occurring at 4,000 IU/kg of body weight daily for 6–15 months. However, liver toxicities can occur at levels as low as 15,000 IU per day to 1.4 million IU per day, with an average daily toxic dose of 120,000 IU per day, particularly with excessive consumption of alcohol. In people with renal failure, 4000 IU can cause substantial damage. In addition, excessive alcohol intake can increase toxicity. Children can reach toxic levels at 1,500 IU/kg of body weight.

Excessive vitamin A consumption can lead to nausea, irritability, anorexia (reduced appetite), vomiting, blurry vision, headaches, hair loss, muscle and abdominal pain and weakness, drowsiness, and altered mental status. In chronic cases, hair loss, dry skin, drying of the mucous membranes, fever, insomnia, fatigue, weight loss, bone fractures, anemia, and diarrhea can all be evident on top of the symptoms associated with less serious toxicity. Some of these symptoms are also common to acne treatment with Isotretinoin. Chronically high doses of vitamin A, and also pharmaceutical retinoids such as 13-cis retinoic acid, can produce the syndrome of pseudotumor cerebri. This syndrome includes headache, blurring of vision and confusion, associated with increased intracerebral pressure. Symptoms begin to resolve when intake of the offending substance is stopped.

An estimated 75% of people in developed nations may be ingesting more than the RDA for vitamin A on a regular basis. Chronic intake of 1500 RAE of preformed vitamin A may be associated with osteoporosis and hip fractures. This may be due to the fact that an excess of vitamin A can block the expression of certain proteins dependent on vitamin K to reduce the efficacy of vitamin D, but has not yet been proven. High vitamin A intake has been associated with spontaneous bone fractures in animals. Cell culture studies have linked increased bone resorption and decreased bone formation with high intakes. This interaction may occur because vitamins A and D may compete for the same receptor and then interact with parathyroid hormone, which regulates calcium. Indeed, a study by Forsmo *et al.* shows a correlation between low bone mineral density and too high intake of vitamin A.

Toxic effects of vitamin A have been shown to significantly affect developing fetuses. Therapeutic doses used for acne treatment have been shown to disrupt cephalic neural cell activity. The fetus is particularly sensitive to vitamin A toxicity during the period of organogenesis. These toxicities only occur with preformed (retinoid) vitamin A (such as from liver). The carotenoid forms (such as beta-carotene as found in carrots), give no such symptoms, except with supplements and chronoic alcoholism, but excessive dietary intake of beta-carotene can lead to carotenodermia, which causes orange-yellow discoloration of the skin.

Smokers and chronic alcohol consumers have been observed to have increased risk of mortality due to lung cancer, esophageal cancer, gastrointestinal cancer and colon cancer. Hepatic (liver) injury been found in human and animal studies where consumption of alcohol is paired with high dose vitamin A and beta-carotene supplementation.

Researchers have succeeded in creating water-soluble forms of vitamin A, which they believed could reduce the potential for toxicity. However, a 2003 study found water-soluble vitamin A was approximately 10 times as toxic as fat-soluble vitamin. A 2006 study found children given water-soluble vitamin A and D, which are typically fat-soluble, suffer from asthma twice as much as a control group supplemented with the fat-soluble vitamins.

Vitamin A and derivatives in medical use

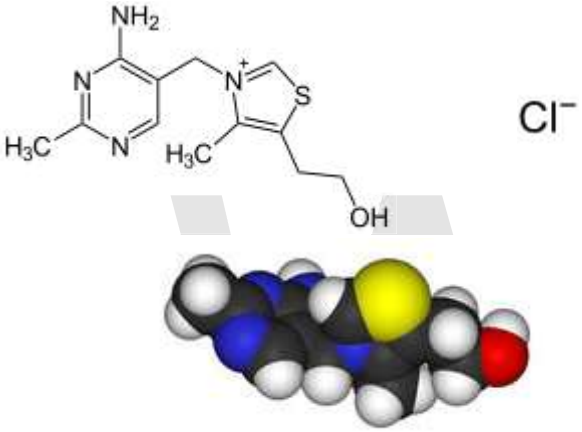
Retinyl palmitate has been used in skin creams, where it is broken down to retinoic acid, which has potent biological activity, as described above.

The retinoids, (for example, 13-cis-retinoic acid), constitute a class of chemical compounds chemically related to retinoic acid, and are used in medicine to modulate gene functions in place of this compound. Like retinoic acid, the related compounds do not have full vitamin A activity, but do have powerful effects on gene expression and epithelial cell differentiation.

Pharmaceutics utilizing mega doses of naturally occurring retinoic acid derivatives are currently in use for cancer, HIV, and dermatological purposes. At high doses, side-effects are similar to vitamin A toxicity. Severe side effects related to vitamin A toxicity, and a small optimal range of use are key obstacles in developing vitamin A-derived pharmaceutics for therapeutic use.

Chapter- 6

Thiamine

Thiamine chloride	
	
IUPAC name 2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl] ethanol	
Other names Aneurine hydrochloride, thiamin	
Identifiers	
CAS number	59-43-8 (Cl^-) ✓, 67-03-8 (Cl^-.HCl hydrochloride)
PubChem	6042
ChemSpider	5819 ✓
UNII	X66NSO3N35 ✓
KEGG	D08580 ✗
MeSH	Thiamine
Properties	
Molecular formula	$C_{12}H_{17}N_4OS^+Cl^-.HCl$
Molar mass	337.27
Melting point	248-260 °C (hydrochloride salt)
Hazards	
Main hazards	Allergies

Thiamine or **thiamin** or **vitamin B_1** and named as the "thio-vitamine" ("sulfur-containing vitamin") is a water-soluble vitamin of the B complex. First named *aneurin*

for the detrimental neurological effects of its lack in the diet, it was eventually assigned the generic descriptor name vitamin B_1. Its phosphate derivatives are involved in many cellular processes. The best-characterized form is thiamine pyrophosphate (TPP), a coenzyme in the catabolism of sugars and amino acids. In yeast, TPP is also required in the first step of alcoholic fermentation.

All living organisms use thiamine in their biochemistry, but it is synthesized in bacteria, fungi, and plants. Animals must obtain it from their diet, and, thus, for them it is a vitamin. Insufficient intake in birds produces a characteristic polyneuritis, and in mammals results in a disease called beriberi affecting the peripheral nervous system (polyneuritis) and/or the cardiovascular system, with fatal outcome if not cured by thiamine administration. In less severe deficiency, nonspecific signs include malaise, weight loss, irritability and confusion.

There is still much work devoted to elucidating the exact mechanisms by which thiamine deficiency leads to the specific symptoms observed (see below). New thiamine phosphate derivatives have recently been discovered, emphasizing the complexity of thiamine metabolism and the need for more research in the field.

Thiamine derivatives with improved pharmacokinetics have been discovered and are to be considered more effective in alleviating the symptoms of thiamine deficiency and other thiamine-related conditions such as impaired glucose metabolism in diabetes. These compounds include allithiamine, prosultiamine, fursultiamine, benfotiamine, and sulbutiamine, among others.

History: The discovery of vitamins and the biochemical lesion

Thiamine was the first of the water-soluble vitamins to be described, leading to the discovery of more such trace compounds essential for survival and to the notion of vitamin.

In 1884, Kanehiro Takaki (1849–1920), a surgeon general in the Japanese navy, rejected the previous germ theory for beriberi and attributed the disease to insufficient diet instead. Switching diet on navy ships, he discovered that substituting white rice with brown barley rice will eliminate beriberi (he was nicknamed "Barley Baron" after obtaining peerage). However, he incorrectly attributed the benefit to nitrogen intake as vitamin was unknown substance at the time.

In 1897, Christiaan Eijkman (1858–1930), a military doctor in the Dutch Indies, discovered that fowl fed on a diet of cooked, polished rice developed paralysis, which could be reversed by discontinuing rice polishing. He attributed that to a nerve poison in the endosperm of rice, from which the outer layers of the grain gave protection to the body. Eijkman was awarded the Nobel Prize in Physiology and Medicine in 1929, because his observations led to the discovery of vitamins. An associate, Gerrit Grijns (1865–1944), correctly interpreted the connection between excessive consumption of

polished rice and beriberi in 1901: He concluded that rice contains an essential nutrient in the outer layers of the grain that is removed by polishing.

In 1911, Casimir Funk isolated an antineuritic substance from rice bran that he called a "vitamine" (on account of its containing an amino group). Dutch chemists, Barend Coenraad Petrus Jansen (1884–1962) and his closest collaborator Willem Frederik Donath (1889–1957), went on to isolate and crystallize the active agent in 1926, whose structure was determined by Robert Runnels Williams (1886–1965), a US chemist, in 1934. Thiamine ("sulfur-containing vitamin") was synthesized in 1936 by the same group.

It was first named "aneurin" (for anti-neuritic vitamin). Sir Rudolph Peters, in Oxford, introduced thiamine-deprived pigeons as a model for understanding how thiamine deficiency can lead to the pathological-physiological symptoms of beriberi. Indeed, feeding the pigeons upon polished rice leads to an easily recognizable behavior of head retraction, a condition called opisthotonos. If not treated, the animal will die after a few days. Administration of thiamine at the stage of opithotonos will lead to a complete cure of the animal within 30 min. As no morphological modifications were observed in the brain of the pigeons before and after treatment with thiamine, Peeters introduced the concept of biochemical lesion

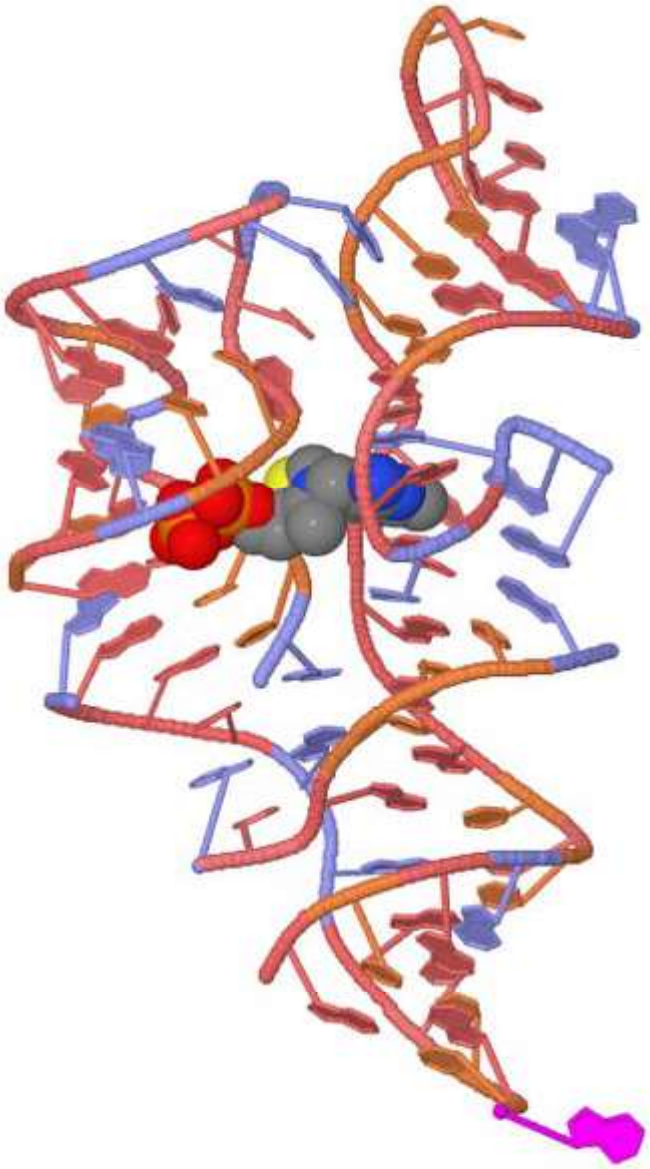
When Lohman and Schuster (1937) showed that the diphosphorylated thiamine derivative (thiamine diphosphate, ThDP) was a cofactor required for the oxydative decarboxylation of pyruvate, (a reaction now known to be catalyzed by pyruvate dehydrogenase), the mechanism of action of thiamine in the cellular metabolism seemed to be elucidated. At present, this view seems to be oversimplified: Pyruvate dehydrogenase is only one of several enzymes requiring thiamine diphosphate as a cofactor; moreover, other thiamine phosphate derivatives have been discovered since then, and they may also contribute to the symptoms observed during thiamine deficiency.

Finally, the mechanism by which the thiamine moiety of ThDP exerts its coenzyme function by proton substitution on position 2 of the thiazolium ring was elucidated by Ronald Breslow in 1958.

Chemical properties

Thiamine is a colorless compound with a chemical formula $C_{12}H_{17}N_4OS$. Its structure contains a pyrimidine ring and a thiazole ring linked by a methylene bridge. Thiamine is soluble in water, methanol, and glycerol and practically insoluble in acetone, ether, chloroform, and benzene. It is stable at acidic pH, but is unstable in alkaline solutions. Thiamine is unstable to heat, but stable during frozen storage. It is unstable when exposed to ultraviolet light and gamma irradiation. Thiamine reacts strongly in Maillard-type reactions.

Biosynthesis



A 3D representation of the TPP riboswitch with thiamine bound

Complex thiamine biosynthetic pathways occur in bacteria, some protozoans, plants and fungi. The thiazole and pyrimidine moieties are synthesized separately and then assembled to form ThMP by thiamine-phosphate synthase (EC 2.5.1.3). The exact biosynthetic pathways may differ among organisms. In E. coli and other enterobacteriaceae ThMP may be phosphorylated to the cofactor ThDP by a thiamine-phosphate kinase (ThMP + ATP → ThDP + ADP, EC 2.7.4.16). In most bacteria and in eukaryotes, ThMP is hydrolyzed to thiamine, that may then be pyrophosphorylated to ThDP by thiamine diphosphokinase (thiamine + ATP → ThDP + AMP, EC 2.7.6.2).

The biosynthetic pathways are regulated by riboswitches in all organisms that synthesise thiamine. If there is sufficient thiamine present in the cell then the thiamine binds to the mRNA encoding genes required in the pathway preventing the translation of the enzymes. If there is no thiamine present then there is no inhibition, and the enzymes required for the biosynthesis are produced. The specific riboswitch, the TPP riboswitch, is the only riboswitch identified in both eukaryotic and prokaryotic organisms.

Nutrition

Occurrence in foods

Thiamine is found in a wide variety of foods at low concentrations. Yeast, yeast extract (e.g. Marmite) and pork are the most highly concentrated sources of thiamine. In general, cereal grains are the most important dietary sources of thiamine, by virtue of their ubiquity. Of these, whole grains contain more thiamine than refined grains, as thiamine is found mostly in the outer layers of the grain and in the germ (which are removed during the refining process). For example, 100 g of whole-wheat flour contains 0.55 mg of thiamine, while 100 g of white flour contains only 0.06 mg of thiamine. In the US, processed flour must be enriched with thiamine mononitrate (along with niacin, ferrous iron, riboflavin, and folic acid) to replace that lost in processing. A whole foods diet is therefore recommended for deficiency.

Some other foods rich in thiamine are oatmeal, flax, and sunflower seeds, brown rice, whole grain rye, asparagus, kale, cauliflower, potatoes, oranges, liver (beef, pork and chicken), and eggs.

Thiamine hydrochloride (Betaxin) is a (when by itself) white, crystalline hygroscopic food-additive used to add a brothy/meaty flavor to gravies or soups. It is a natural intermediary resulting from a thiamine-HCl reaction, which precedes hydrolysis and phosphorylation, before it is finally employed (in the form of TPP) in a number of enzymatic amino, fatty acid, and carbohydrate reactions.

Reference Daily Intake and high doses

The RDA in most countries is set at about 1.4 mg. However, tests on female volunteers at daily doses of about 50 mg have claimed an increase in mental acuity. There are no reports available of adverse effects from consumption of excess thiamine by ingestion of food and supplements. Because the data is inadequate for a quantitative risk assessment, no Tolerable Upper Intake Level (UL) can be derived for thiamine.

Antagonists

Thiamine in foods can be degraded in a variety of ways. Sulfites, which are added to foods usually as a preservative, will attack thiamine at the methylene bridge in the structure, cleaving the pyrimidine ring from the thiazole ring. The rate of this reaction is increased under acidic conditions. Thiamine is degraded by thermolabile thiaminases

(present in raw fish and shellfish). Some thiaminases are produced by bacteria. Bacterial thiaminases are cell surface enzymes that must dissociate from the membrane before being activated; the dissociation can occur in ruminants under acidotic conditions. Rumen bacteria also reduce sulfate to sulfite, therefore high dietary intakes of sulfate can have thiamine-antagonistic activities.

Plant thiamine antagonists are heat-stable and occur as both the ortho- and para-hydroxyphenols. Some examples of these antagonists are caffeic acid, chlorogenic acid, and tannic acid. These compounds interact with the thiamine to oxidize the thiazole ring, thus rendering it unable to be absorbed. Two flavonoids, quercetin and rutin, have also been implicated as thiamine antagonists.

Absorption and transport

Absorption

Thiamine is released by the action of phosphatase and pyrophosphatase in the upper small intestine. At low concentrations, the process is carrier mediated and at higher concentrations, absorption occurs via passive diffusion. Active transport is greatest in the jejunum and ileum (it is inhibited by alcohol consumption and by folic deficiency). Decline in thiamine absorption occurs at intakes above 5 mg. The cells of the intestinal mucosa have thiamine pyrophosphokinase activity, but it is unclear whether the enzyme is linked to active absorption. The majority of thiamine present in the intestine is in the pyrophosphorylated form ThDP, but when thiamine arrives on the serosal side of the intestine it is often in the free form. The uptake of thiamine by the mucosal cell is likely coupled in some way to its phosphorylation/dephosphorylation. On the serosal side of the intestine, evidence has shown that discharge of the vitamin by those cells is dependent on Na^+-dependent ATPase.

Bound to serum proteins

The majority of thiamine in serum is bound to proteins, mainly albumin. Approximately 90% of total thiamine in blood is in erythrocytes. A specific binding protein called thiamine-binding protein (TBP) has been identified in rat serum and is believed to be a hormonally regulated carrier protein that is important for tissue distribution of thiamine.

Cellular uptake

Uptake of thiamine by cells of the blood and other tissues occurs via active transport and passive diffusion. About 80% of intracellular thiamine is phosphorylated and most is bound to proteins. In some tissues, thiamine uptake and secretion appears to be mediated by a soluble thiamine transporter that is dependent on Na^+ and a transcellular proton gradient.

Tissue distribution

Human storage of thiamine is about 25 to 30 mg with the greatest concentrations in skeletal muscle, heart, brain, liver, and kidneys. ThMP and free (unphosphorylated) thiamine is present in plasma, milk, cerebrospinal fluid, and likely all extracellular fluids. Unlike the highly phosphorylated forms of thiamine, ThMP and free thiamine are capable of crossing cell membranes. Thiamine contents in human tissues are less than those of other species.

Excretion

Thiamine and its acid metabolites (2-methyl-4-amino-5-pyrimidine carboxylic acid, 4-methyl-thiazole-5-acetic acid and thiamine acetic acid) are excreted principally in the urine.

Thiamine phosphate derivatives and function

Thiamine is mainly the transport form of the vitamin, while the active forms are phosphorylated thiamine derivatives. There are four known natural thiamine phosphate derivatives: thiamine monophosphate (ThMP), thiamine diphosphate (ThDP), also sometimes called thiamine pyrophosphate (TPP), thiamine triphosphate (ThTP), and the recently discovered adenosine thiamine triphosphate (AThTP) and adenosine thiamine diphosphate (AThDP).

Thiamine monophosphate

There is no known physiological role of ThMP.

Thiamine diphosphate

The synthesis of thiamine diphosphate (ThDP), also known as *thiamine pyrophosphate* (TPP) or *cocarboxylase*, is catalyzed by an enzyme called thiamine diphosphokinase according to the reaction thiamine + ATP → ThDP + AMP (EC 2.7.6.2). ThDP is a coenzyme for several enzymes that catalyze the transfer of two-carbon units and in particular the dehydrogenation (decarboxylation and subsequent conjugation with coenzyme A) of 2-oxoacids (alpha-keto acids). Examples include:

- Present in most species
  - pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase (also called α-ketoglutarate dehydrogenase)
  - branched-chain α-keto acid dehydrogenase
  - 2-hydroxyphytanoyl-CoA lyase
  - transketolase

- Present in some species:
  - pyruvate decarboxylase (in yeast)

- several additional bacterial enzymes

The enzymes transketolase, pyruvate dehydrogenase (PDH) and 2-oxoglutarate dehydrogenase (OGDH) are all important in carbohydrate metabolism. The cytosolic enzyme transketolase is a key player in the pentose phosphate pathway, a major route for the biosynthesis of the pentose sugars deoxyribose and ribose. The mitochondrial PDH and OGDH are part of biochemical pathways that result in the generation of adenosine triphosphate (ATP), which is a major form of energy for the cell. PDH links glycolysis to the citric acid cycle, while the reaction catalyzed by OGDH is a rate-limting step in the citric acid cycle. In the nervous system, PDH is also involved in the production of acetylcholine, a neurotransmitter, and for myelin synthesis.

Thiamine triphosphate

Thiamine triphosphate (ThTP) was long considered a specific neuroactive form of thiamine. However, recently it was shown that ThTP exists in bacteria, fungi, plants and animals suggesting a much more general cellular role. In particular in *E. coli*, it seems to play a role in response to amino acid starvation.

Adenosine thiamine triphosphate

Adenosine thiamine triphosphate (AThTP) or thiaminylated adenosine triphosphate has recently been discovered in *Escherichia coli* where it accumulates as a result of carbon starvation. In *E. coli*, AThTP may account for up to 20% of total thiamine. It also exists in lesser amounts in yeast, roots of higher plants and animal tissue.

Adenosine thiamine diphosphate

Adenosine thiamine diphosphate (AThDP) or thiaminylated adenosine diphosphate exists in small amounts in vertebrate liver, but its role remains unknown.

Deficiency

Thiamine derivatives and thiamine-dependent enzymes are present in all cells of the body, thus, a thiamine deficiency would seem to adversely affect all of the organ systems. However, the nervous system and the heart are particularly sensitive to thiamine deficiency, because of their high oxidative metabolism.

Thiamine deficiency can lead to severe fatigue of eyes and myriad problems including neurodegeneration, wasting, and death. A lack of thiamine can be caused by malnutrition, a diet high in thiaminase-rich foods (raw freshwater fish, raw shellfish, ferns) and/or foods high in anti-thiamine factors (tea, coffee, betel nuts) and by grossly impaired nutritional status associated with chronic diseases, such as alcoholism, gastrointestinal diseases, HIV-AIDS, and persistent vomiting. It is thought that many people with diabetes have a deficiency of thiamine and that this may be linked to some of the complications that can occur.

Well-known syndromes caused by thiamine deficiency include beriberi and Wernicke-Korsakoff syndrome, diseases also common with chronic alcoholism.

Beriberi

Beriberi is a neurological and cardiovascular disease. The three major forms of the disorder are dry beriberi, wet beriberi, and infantile beriberi.

- *Dry beriberi* is characterized principally by peripheral neuropathy consisting of symmetric impairment of sensory, motor, and reflex functions affecting distal more than proximal limb segments and causing calf muscle tenderness.
- *Wet beriberi* is associated with mental confusion, muscular atrophy, edema, tachycardia, cardiomegaly, and congestive heart failure in addition to peripheral neuropathy.
- *Infantile beriberi* occurs in infants breast-fed by thiamin-deficient mothers (who may show no sign of thiamine deficiency). Infants may manifest cardiac, aphonic, or pseudomeningitic forms of the disorder. Infants with cardiac beriberi frequently exhibit a loud piercing cry, vomiting, and tachycardia. Convulsions are not uncommon, and death may ensue if thiamine is not administered promptly.

Following thiamine treatment, rapid improvement occurs, in general, within 24 hours. Improvements of peripheral neuropathy may require several months of thiamine treatment.

Alcoholic brain disease

Nerve cells and other supporting cells (such as glial cells) of the nervous system require thiamine. Examples of neurologic disorders that are linked to alcohol abuse include Wernicke's encephalopathy (WE, Wernicke-Korsakoff syndrome) and Korsakoff's psychosis (alcohol amnestic disorder) as well as varying degrees of cognitive impairment.

Wernicke's encephalopathy is the most frequently encountered manifestation of thiamine deficiency in Western society, though it may also occur in patients with impaired nutrition from other causes, such as gastrointestinal disease, those with HIV-AIDS, and with the injudicious administration of parenteral glucose or hyperalimentation without adequate B-vitamin supplementation. This is a striking neuro-psychiatric disorder characterized by paralysis of eye movements, abnormal stance and gait, and markedly deranged mental function.

Alcoholics may have thiamine deficiency because of the following:

- Inadequate nutritional intake: Alcoholics tend to intake less than the recommended amount of thiamine.
- Decreased uptake of thiamine from the GI tract: Active transport of thiamine into enterocytes is disturbed during acute alcohol exposure.
- Liver thiamine stores are reduced due to hepatic steatosis or fibrosis.

- Impaired thiamine utilization: Magnesium, which is required for the binding of thiamine to thiamine-using enzymes within the cell, is also deficient due to chronic alcohol consumption. The inefficient utilization of any thiamine that does reach the cells will further exacerbate the thiamine deficiency.
- Ethanol *per se* inhibits thiamine transport in the gastrointestinal system and blocks phosphorylation of thiamine to its cofactor form (ThDP).

Korsakoff Psychosis is, in general, considered to occur with deterioration of brain function in patients initially diagnosed with WE. This is an amnestic-confabulatory syndrome characterized by retrograde and anterograde amnesia, impairment of conceptual functions, and decreased spontaneity and initiative.<

Following improved nutrition and the removal of alcohol consumption, some impairments linked with thiamine deficiency are reversed; particularly poor brain functionality, although in more severe cases, Wernicke-Korsakoff syndrome leaves permanent damage.

Thiamine deficiency in poultry

As most feedstuffs used in poultry diets contain enough quantities of vitamins to meet the requirements in this species, deficiencies in this vitamin do not occur with commercial diets. This was, at least, the opinion in the 1960s.

Mature chickens show signs 3 weeks after being fed a deficient diet. In young chicks, it can appear before 2 weeks of age.

Onset is sudden in young chicks. There is anorexia and an unsteady gait. Later on, there are locomotor signs, beginning with an apparent paralysis of the flexor of the toes. The characteristic position is called "stargazing", meaning a chick "sitting on its hocks and the head in opisthotonos".

Response to administration of the vitamin is rather quick, occurring a few hours later.

Differential diagnosis include riboflavin deficiency and avian encephalomyelitis. In riboflavin deficiency, the "curled toes" is a characteristic symptom. Muscle tremor is typical of avian encephalomyelitis. A therapeutic diagnosis can be tried by supplementing thiamine only in the affected bird. If the animals do not respond in a few hours, thiamine deficiency can be excluded.

Thiamine deficiency in ruminants

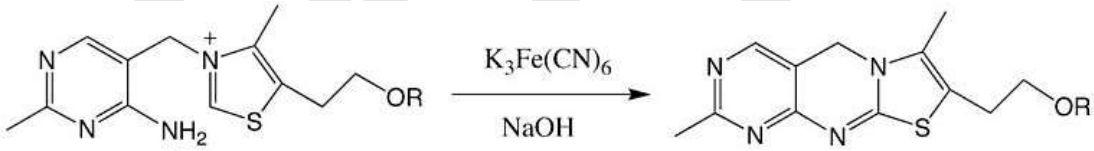
Polioencephalomalacia (PEM) is the most common thiamine deficiency disorder in young ruminant and nonruminant animals. Symptoms of PEM include a profuse, but transient, diarrhea, listlessness, circling movements, star gazing or opisthotonus (head drawn back over neck), and muscle tremors. The most common cause is high-carbohydrate feeds, leading to the overgrowth of thiaminase-producing bacteria, but

dietary ingestion of thiaminase (e.g., in bracken fern), or inhibition of thiamine absorption by high sulfur intake are also possible. Another cause of PEM is *Clostridium sporogenes* or *Bacillus aneurinolyticus* infection. These bacteria produce thiaminases that will cause an acute thiamine deficiency in the affected animal.

Idiopathic paralytic disease in wild birds

Recently, thiamine deficiency has been identified as the cause of a paralytic disease affecting wild birds in the Baltic Sea area dating back to 1982. In this condition, there is difficulty in keeping the wings folded along the side of the body when resting, loss of the ability to fly and voice, with eventual paralysis of the wings and legs and death. It affects primarily 0.5–1 kg sized birds such as the herring gull (Larus argentatus), Common Starling (Sturnus vulgaris) and Common Eider (Somateria mollissima). Researches noted, "Because the investigated species occupy a wide range of ecological niches and positions in the food web, we are open to the possibility that other animal classes may suffer from thiamine deficiency as well."

Analysis and diagnostic testing



R = H	Thiamine	Thiochrome
R = PO_3^{2-}	ThMP	ThcMP
R = $P_2O_6^{3-}$	ThDP	ThcDP
R = $P_3O_9^{4-}$	ThTP	ThcTP
R = $P_3O_8^{3-}$-adénosine	AThTP	AThcTP

Oxidation of thiamine derivatives to fluorescent thiochromes by potassium ferricyanide under alkaline conditions

A positive diagnosis test for thiamine deficiency can be ascertained by measuring the activity of the enzyme transketolase in erythrocytes (Erythrocyte Transketolase Activation Assay). Thiamine, as well as its phosphate derivatives, can also be detected directly in whole blood, tissues, foods, animal feed, and pharmaceutical preparations following the conversion of thiamine to fluorescent thiochrome derivatives (Thiochrome Assay) and separation by high-performance liquid chromatography (HPLC). In recent reports, a number of Capillary Electrophoresis (CE) techniques and in-capillary enzyme reaction methods have emerged as potential alternative techniques for the determination and monitoring of thiamine in samples.

Genetic diseases

Genetic diseases of thiamine transport are rare but serious. Thiamine responsive megaloblastic anemia (TRMA) with diabetes mellitus and sensorineural deafness is an autosomal recessive disorder caused by mutations in the gene SLC19A2, a high affinity thiamine transporter. TRMA patients do not show signs of systemic thiamine deficiency, suggesting redundancy in the thiamine transport system. This has led to the discovery of a second high-affinity thiamine transporter, SLC19A3. Leigh disease (subacute necrotising encephalomyelopathy) is an inherited disorder that affects mostly infants in the first years of life and is invariably fatal. Pathological similarities between Leigh disease and WE led to the hypothesis that the cause was a defect in thiamine metabolism. One of the most consistent findings has been an abnormality of the activation of the pyruvate dehydrogenase complex.

Other disorders in which a putative role for thiamine has been implicated include subacute necrotizing encephalomyelopathy, opsoclonic cerebellopathy (a paraneoplastic syndrome), and Nigerian seasonal ataxia. In addition, several inherited disorders of ThDP-dependent enzymes have been reported, which may respond to thiamine treatment.

Research

Research in the field mainly concerns the mechanisms by which thiamine deficiency leads to neuronal death in relation to Wernicke Korsakoff Psychosis. Another important field concerns the understanding of the molecular mechanisms involved in ThDP catalysis. More recently, research has been devoted to the understanding of the possible non-cofactor roles of other derivatives such as ThTP and AThTP.

Understanding the mechanism by which thiamine deficiency leads to selective neuronal death

Experimentally induced beriberi polyneuropathy in chickens may be a good model for studying these forms of neuropathy in view of diagnosis and treatment. From studies using rat models, a link between thiamine deficiency and colon carcinogenesis was suggested. Rat model is used also in research of Wernicke's encephalopathy. Thiamine deprived mice are a classic model of systemic oxidative stress, used in research of Alzheimer’s disease.

Catalytic mechanisms in thiamine diphosphate-dependent enzymes

A lot of work is devoted to the understanding of the interplay between ThDP and ThDP-dependent enzymes in catalysis.

Non-cofactor roles of thiamine derivatives

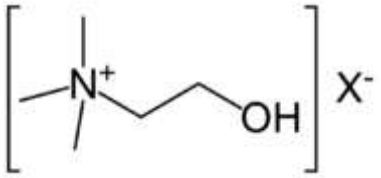
Thiamine compounds other than ThDP exist in most cells from many organisms, including bacteria, fungi, plants and animals. Among those compounds are thiamine triphosphate (ThTP) and adenosine thiamine triphosphate (AThTP) are thought to have non-cofactor roles, though at present it is not known to what extent they participate in the symptoms

Persistent carbenes

The production of furoin from furfural is catalyzed by thiamine through a relatively stable carbene (an organic molecule containing unbonded valence electrons pairs at a carbon center). This reaction, studied in 1957 by R. Breslow, was the first evidence for the existence of persistent carbenes.

Chapter- 7

Choline

Choline	
	
Other names	
Bilineurine	
Identifiers	
CAS number	62-49-7
PubChem	305
ChemSpider	299
KEGG	C00114
ChEMBL	CHEMBL920
Properties	
Molecular formula	$C_5H_{14}NO$
Molar mass	104.17 g mol^{-1}

Choline is a water-soluble essential nutrient. It is usually grouped within the B-complex vitamins. Choline generally refers to the various quaternary ammonium salts containing the *N*,*N*,*N*-trimethylethanolammonium cation.

The cation appears in the head groups of phosphatidylcholine and sphingomyelin, two classes of phospholipid that are abundant in cell membranes. It also becomes the neurotransmitter acetylcholine.

History

Choline was discovered by Adolph Strecker in 1864 and chemically synthesized in 1866. In 1998 choline was classified as an essential nutrient by the Food and Nutrition Board of the Institute of Medicine (U.S.A.).

Chemistry

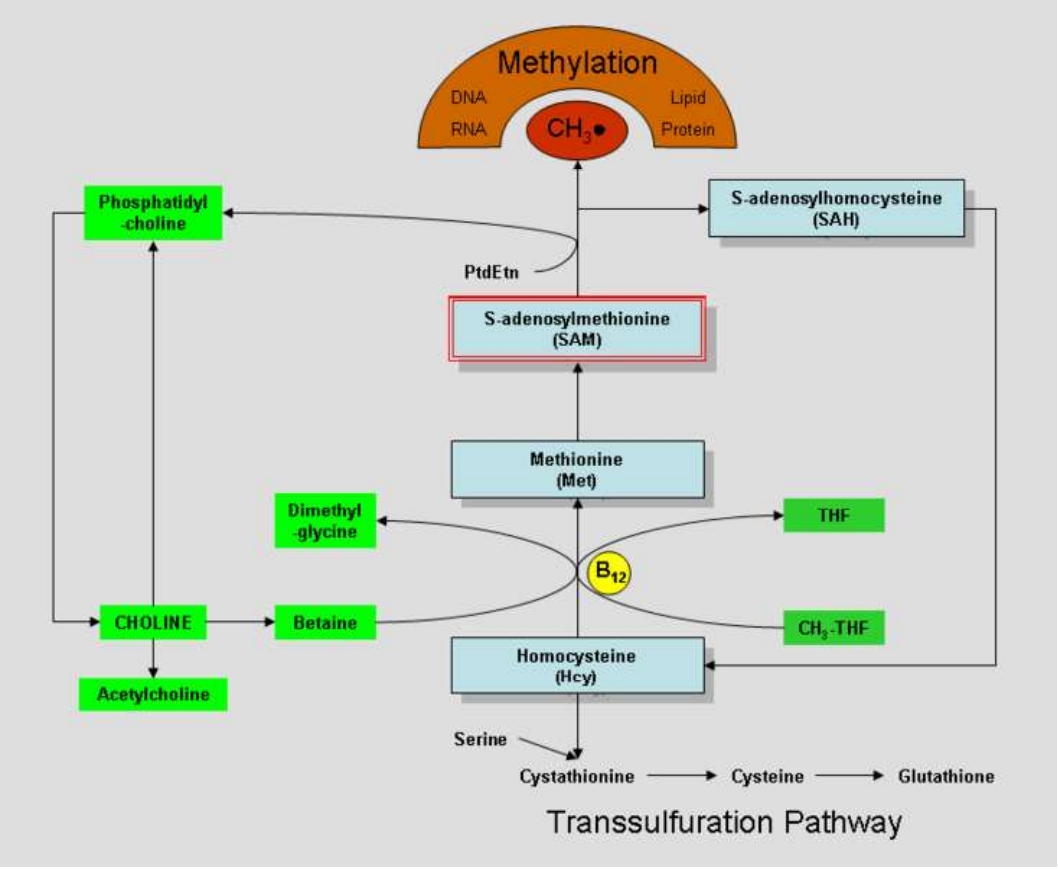
Choline is a quaternary saturated amine with the chemical formula $(CH_3)_3N^+CH_2CH_2OHX^-$, where X^- is a counterion such as chloride, hydroxide or tartrate. Choline chloride can form a low-melting deep eutectic solvent mixture with urea with unusual properties. The salicylate salt is used topically for pain relief of aphthous ulcers.

Choline hydroxide

Choline hydroxide is one of the class of phase transfer catalysts that are used to carry the hydroxide ion into organic systems, and, therefore, is considered a strong base. It is the least costly phase transfer catalyst, and is used as a cheap method of stripping photoresists in circuit boards. Choline hydroxide is not completely stable, and it slowly breaks down into trimethylamine.

Role in humans

Physiology



Choline metabolism. (Choline is green box at left, second from the bottom.)

Choline and its metabolites are needed for three main physiological purposes: structural integrity and signaling roles for cell membranes, cholinergic neurotransmission (acetylcholine synthesis), and a major source for methyl groups via its metabolite, trimethylglycine (betaine) that participates in the S-adenosylmethionine synthesis pathways.

Fish odor syndrome

Choline is a precursor to trimethylamine, which some persons are not able to break down due to a genetic disorder called trimethylaminuria. Persons suffering from this disorder may suffer from a strong fishy or otherwise unpleasant body odor, due to the body's release of odorous trimethylamine. A body odor will occur even on a normal diet – *i.e.*, one that is not particularly high in choline. Persons with trimethylaminuria are advised to restrict the intake of foods high in choline; this may help to reduce the sufferer's body odor.

Food sources of choline

The Adequate Intake (AI) of choline is 425 mg (milligrams) per day for adult women; higher for pregnant and breastfeeding women. The AI for adult men is 550 mg/day. There are also AIs for children and teens.

Animal and plant foods	Choline (mg)	Calories
5 ounces (142 g) raw beef liver	473	192
Large hardboiled egg	113	78
Half a pound (227 g) cod fish	190	238
Half a pound of chicken	149	270
Quart of milk, 1% fat	173	410
A tablespoon (8 g) soy lecithin	250 approx.	60
A pound (454 grams) of cauliflower	177	104
A pound of spinach	113	154
A cup of wheat germ	202	432
Two cups (0.47 liters) firm tofu	142	353
Two cups of cooked kidney beans	108	450.
A cup of uncooked quinoa	119	626.
A cup of uncooked amaranth	135	716
A grapefruit	19	103
3 cups (710 cc) cooked brown rice	54	649
A cup (146 g) of peanuts	77	828
A cup (143 g) of almonds	74	822

Besides cauliflower, other cruciferous vegetables may also be good sources of choline.

Choline and other nutrient values for many foods can be obtained online.

Groups at risk for choline deficiency

Vegetarians, vegans, endurance athletes, and people who drink a lot of alcohol may be at risk for choline deficiency and may benefit from choline supplements.

In general, people who do not eat many whole eggs may have to pay close attention to get enough choline in their diets. Studies on a number of different populations have found that the average intake of choline was below the Adequate Intake (AI).

The choline researcher Dr. Steven Zeisel wrote: "A recent analysis of data from NHANES 2003–2004 revealed that for [American] older children, men, women and pregnant women, mean choline intakes are far below the AI. Ten percent or fewer had usual choline intakes at or above the AI."

Health effects of dietary choline

Choline deficiency may play a role in liver disease, atherosclerosis, and possibly neurological disorders, One symptom of choline deficiency is an elevated level of the liver enzyme ALT.

It is particularly important for pregnant women to get enough choline, since low choline intake may raise the rate of neural tube defects in infants, and may affect their child's memory. One study found that higher dietary intake of choline shortly before and after conception was associated with a lower risk of neural tube defects. If low choline intake causes an elevated homocysteine level, it raises the risk for preeclampsia, premature birth, and very low birth weight.

Women with diets richer in choline may have a lower risk for breast cancer, but other studies found no association.

There is some evidence to suggest that choline is anti-inflammatory. In the ATTICA study, higher dietary intake of choline was associated with lower levels of inflammatory markers. A small study found that choline supplements reduced symptoms of allergic rhinitis.

Despite its importance in the central nervous system as a precursor for acetylcholine and membrane phosphatidylcholine, the role of choline in mental illness has been little studied. In a large population-based study, blood levels of choline were inversely correlated with anxiety symptoms in subjects aged 46–49 and 70–74 years. However, there was no correlation between depression and choline level in this study.

The Adequate Intake is intended to be high enough to be adequate for almost all healthy people. Many people do not develop deficiency symptoms when consuming less than the Adequate Intake of choline. The human body synthesizes some of the choline it needs,

and people vary in their need for dietary choline. In one study, premenopausal women were less sensitive to a low-choline diet than men or postmenopausal women.

However, the Adequate Intake may not be enough for some people. In the same study, 6 out of 26 men developed choline deficiency symptoms while consuming the Adequate Intake (and no more) of choline. The Adequate Intake was less than the optimal intake for the male subjects in another study.

High dietary intake of choline was associated with an increased risk of colon adenomas (polyps), for women in the Nurses' Health Study. However, this could represent effects of other components in the foods from which choline was obtained. Dietary choline intake was not associated with increased risk of colorectal cancer, for men in the Health Professionals Follow-up Study.

Choline as a dietary supplement

The most often available choline supplement is lecithin, derived from soy or egg yolks, often used as a food additive. Phosphatidylcholine is also available as a supplement, in pill or powder form. Supplementary choline is also available as choline chloride, which comes as a liquid due to its hydrophilic properties. Choline chloride is sometimes preferred as a supplement because phosphatidylcholine can have gastrointestinal side effects.

It is well established that supplements of methyl group transfer vitamins B_6, B_{12}, folic acid reduce the blood titer of homocysteine and so may prevent heart disease. Choline or betaine supplements also may reduce homocysteine. Choline is a necessary source of methyl groups for methyl group transfer. Supplements of lecithin/choline were found to reduce heart disease in laboratory studies. The reduction in heart disease with lecithin supplements may however relate more to the cholesterol-carrying capacity of lecithin than to the methyl group transfer role of choline.

Choline supplements are often taken as a form of 'smart drug' or nootropic, due to the role that the neurotransmitter acetylcholine plays in various cognition systems within the brain. Choline is a chemical precursor or "building block" needed to produce the neurotransmitter acetylcholine, and research suggests that memory, intelligence, and mood are mediated at least in part by acetylcholine metabolism in the brain. In a study on rats, a correlation was shown between choline intake during pregnancy and mental task performance of the offspring; but the same correlation has not been shown in humans. However, this human study admits that "[w]omen in the current study consumed their usual diets. They were not eating choline-enriched diets and were not receiving choline supplementation. Therefore, our results indicate that choline concentrations in a physiologic range observed among women consuming a regular diet during pregnancy are not related to IQ in their offspring. We cannot rule out the possibility that choline supplementation could have an IQ effect."

The compound's quaternary amine renders it lipid-insoluble, which might suggest it would be unable to cross the blood-brain barrier. However, despite choline's lipid insolubility, a choline transporter that allows transport across the blood-brain barrier exists. The efficacy of these supplements in enhancing cognitive abilities is a topic of continuing debate.

The Food and Drug Administration (FDA) requires that infant formula not made from cow's milk be supplemented with choline.

Due to its role in lipid metabolism, choline has also found its way into nutritional supplements that claim to reduce body fat; but there is little or no evidence to prove that it has any effect on reducing excess body fat, or that taking high amounts of choline will increase the rate at which fat is metabolised.

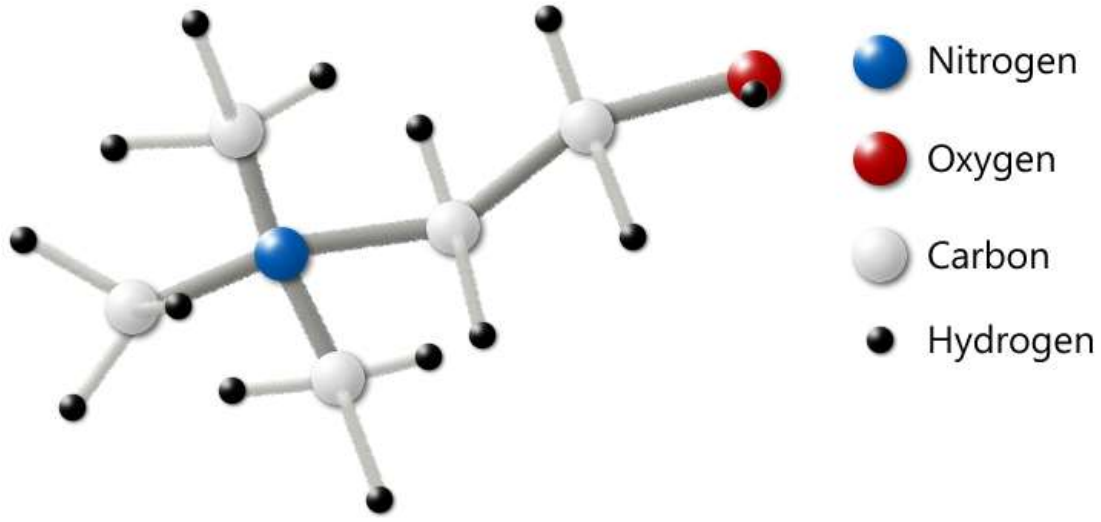
Pharmaceutical uses

Choline is used in the treatment of liver disorders, Alzheimer's disease, and bipolar disorder.

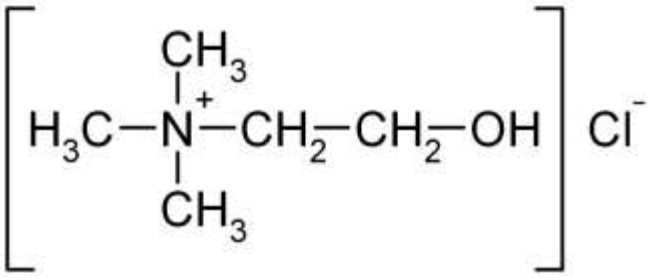
Some studies show that as a supplement, choline is also used in treating hepatitis, glaucoma, atherosclerosis, and, possibly, neurological disorders.

Choline has also been proven to have a positive effect on those suffering from alcoholism.

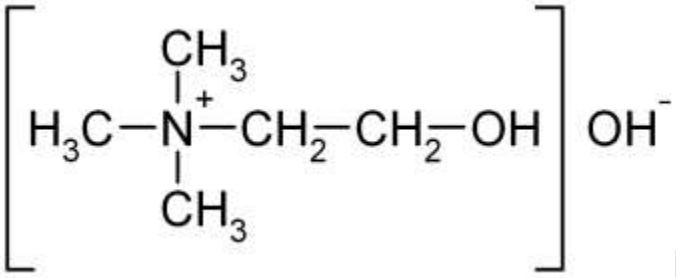
The current NIH funded research study COBRIT is gathering data regarding potential benefit of longterm citicoline treatment for recovery after traumatic brain injury.



Choline ($C_5H_{14}NO^+$)



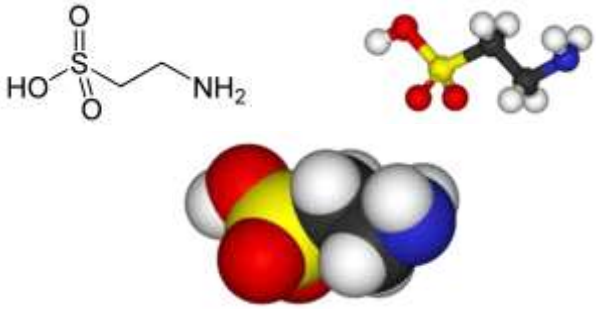
Choline chloride



Choline hydroxide

Chapter- 8

Taurine

Taurine	
	
IUPAC name 2-aminoethanesulfonic acid **Other names** tauric acid	
Identifiers	
CAS number	107-35-7 ✓
PubChem	1123
ChemSpider	1091 ✓
UNII	1EQV5MLY3D ✓
ChEMBL	CHEMBL239243 ✓
IUPHAR ligand	2379
Properties	
Molecular formula	$C_2H_7NO_3S$
Molar mass	125.15 g mol^{-1}
Density	1.734 g/cm^3 (at −173.15 °C)
Melting point	305.11 °C
Acidity (pK_a)	<0, 9.06

Taurine, or **2-aminoethanesulfonic acid**, is an organic acid. It is a major constituent of bile and can be found in the lower intestine and, in small amounts, in the tissues of many animals, including humans. Taurine is a derivative of the sulfur-containing (sulfhydryl) amino acid cysteine. Taurine is one of the few known naturally occurring sulfonic acids.

History

Taurine is named after the Latin *Taurus* (a cognate of the Greek *ταύρος*) which means bull or ox, as it was first isolated from ox bile in 1827 by German scientists Friedrich Tiedemann and Leopold Gmelin. In the strict sense, it is not an amino acid, as it lacks a carboxyl group, but it is often called one, even in scientific literature. It does contain a sulfonate group and may be called an amino sulfonic acid. Small polypeptides have been identified which contain taurine, but to date no aminoacyl tRNA synthetase has been identified as specifically recognizing taurine and capable of incorporating it into a tRNA.

Biosynthesis

Mammalian taurine synthesis occurs in the pancreas via the cysteine sulfinic acid pathway. In this pathway, the sulfhydryl group of cysteine is first oxidized to cysteine sulfinic acid by the enzyme cysteine dioxygenase. Cysteine sulfinic acid, in turn, is decarboxylated by sulfinoalanine decarboxylase to form hypotaurine. It is unclear whether hypotaurine is then spontaneously or enzymatically oxidized to yield taurine.

Chemical synthesis and commercial production

Synthetic taurine is obtained from isethionic acid (2-hydroxyethanesulfonic acid), which in turn is obtained from the reaction of ethylene oxide with aqueous sodium bisulfite. Another approach is the reaction of aziridine with sulfurous acid. This leads directly to taurine.

In 1993, approximately 5,000–6,000 tons of taurine were produced for commercial purposes; 50% for pet food manufacture, 50% in pharmaceutical applications. As of 2010, China alone has more than 40 manufacturers of taurine. Most of these enterprises employ the ethanolamine method to produce a total annual production of about 3,000 tons.

In human nutrition

Physiological functions

Taurine is conjugated via its amino terminal group with chenodeoxycholic acid and cholic acid to form the bile salts sodium taurochenodeoxycholate and sodium taurocholate. The low pKa of taurine's sulfonic acid group ensures that this moiety is negatively charged in the pH ranges normally found in the intestinal tract and, thus, improves the surfactant properties of the cholic acid conjugate. Taurine crosses the blood-brain barrier and has been implicated in a wide array of physiological phenomena including inhibitory neurotransmission, long-term potentiation in the striatum/hippocampus, membrane stabilization, feedback inhibition of neutrophil/macrophage respiratory burst, adipose tissue regulation and possible prevention of obesity, calcium homeostasis, recovery from osmotic shock, protection against glutamate excitotoxicity and prevention of epileptic seizures. It also acts as an

antioxidant and protects against toxicity of various substances (such as lead and cadmium). Additionally, supplementation with taurine has been shown to prevent oxidative stress induced by exercise. In a 2008 study, taurine has been shown to reduce the secretion of apolipoprotein B100 and lipids in HepG2 cells. High concentrations of serum lipids and apolipoprotein B100 (essential structural component of VLDL and LDL) are major risk factors of atherosclerosis and coronary heart disease. Hence, it is possible that taurine supplementation is beneficial for the prevention of these diseases. In a 2003 study, Zhang et al. have demonstrated the hypocholesterolemic (blood cholesterol-lowering) effect of dietary taurine in young overweight adults. Furthermore, they reported that body weight also decreased significantly in the taurine supplemented group. These findings are consistent with animal studies. Taurine has also been shown to help people with congestive heart failure by increasing the force and effectiveness of heart-muscle contractions.

Taurine levels were found to be significantly lower in vegans than in a control group on a standard American diet. Plasma taurine was 78% of control values, and urinary taurine 29%.

In the cell, taurine keeps potassium and magnesium inside the cell while keeping excessive sodium out. In this sense, it works like a diuretic. Because it aids the movement of potassium, sodium, and calcium in and out of the cell, taurine has been used as a supplementation for epileptics as well as for people who have uncontrollable facial twitches.

According to animal studies, taurine produces anxiolytic effect and may act as a modulator or anti-anxiety agent in the central nervous system.

Taurine is necessary for normal skeletal muscle functioning. This was shown by a 2004 study, using mice with a genetic taurine deficiency. They had a nearly complete depletion of skeletal and cardiac muscle taurine levels. These mice had a reduction of more than 80% of exercise capacity compared to control mice. The authors expressed themselves as "surprised" that cardiac function showed as largely normal (given various other studies about effects of taurine on the heart).

Studies have shown that taurine can influence (and possibly reverse) defects in nerve blood flow, motor nerve conduction velocity, and nerve sensory thresholds in experimental diabetic neuropathic rats. In another study on diabetic rats, taurine significantly decreased weight and decreased blood sugar in these animal models. Likewise, a 2008 study demonstrated that taurine administration to diabetic rabbits resulted in 30% decrease in serum glucose levels. According to the single study on human subjects, daily administration of 1.5g taurine had no significant effect on insulin secretion or insulin sensitivity. There is evidence that taurine may exert a beneficial effect in preventing diabetes-associated microangiopathy and tubulointerstitial injury in diabetic nephropathy. Taurine acts as a glycation inhibitor. Studies have shown that taurine treated diabetic rats had a decrease in the formation of advanced glycation end products (AGEs) and AGEs content. The United States Department of Agriculture has found a link

between cataract development and lower levels of vitamin B6, folate, and taurine in the diets of the elderly.

Average daily consumption from food

Taurine occurs naturally in food, especially in seafood and meat. The mean daily intake from omnivore diets was determined to be around 58 mg (range from 9 to 372 mg) and to be low or negligible from a strict vegan diet. In another study, taurine intake was estimated to be generally less than 200 mg/day, even in individuals eating a high-meat diet. According to another study, taurine consumption was estimated to vary between 40 to 400 mg/day.

Energy drinks

Despite being present in many energy foods, taurine has not been proven to be energy-giving. A study of mice hereditarily unable to transport taurine suggests that it is needed for proper maintenance and functioning of skeletal muscles. In addition, it has been shown to be effective in removing fatty liver deposits in rats, preventing liver disease, and reducing cirrhosis in tested animals. There is also evidence that taurine is beneficial for adult human blood pressure and possibly, the alleviation of other cardiovascular ailments (in humans suffering essential hypertension, taurine supplementation resulted in measurable decreases in blood pressure).

Taurine is regularly used as an ingredient in energy drinks, with many containing 1000 mg per serving, and some as much as 2000 mg. A 2003 study by the European Food Safety Authority found no adverse effects for up to 1,000 mg of taurine per kilogram of body weight per day.

A review published in 2008 found no documented reports of negative or positive health effects associated with the amount of taurine used in energy drinks, concluding that "The amounts of guarana, taurine, and ginseng found in popular energy drinks are far below the amounts expected to deliver either therapeutic benefits or adverse events".

Other uses

Lately, cosmetic compositions containing taurine have been introduced, possibly due to its antifibrotic properties. It has been shown that taurine prevents the damaging effects of TGFB1 to hair follicles. It also helps to maintain skin hydration.

It is believed that prematurely born infants lack the enzymes needed to convert cystathionine to cysteine and may, therefore, become deficient in taurine. Thus, taurine has been added to many infant formulas as a measure of prudence, since the early 1980s. However, this practice has never been rigorously studied, and as such it has yet to be proven to be necessary, or even beneficial.

Taurine is also used in some contact lens solutions.

Toxicity

Taurine is involved in a number of crucial physiological processes. However, the role of taurine in these processes is not clearly understood and the influence of high taurine doses on these processes is uncertain. A substantial increase in the plasma concentration of growth hormone was reported in some epileptic patients during taurine tolerance testing (oral dose of 50 mg/kg bw/day), suggesting a potential to stimulate the hypothalamus and to modify neuroendocrine function. There is an indication that taurine (2 g/day) has some function in the maintenance and possibly in the induction of psoriasis. It may also be necessary to take into consideration that absorption of taurine from beverages may be more rapid than from foods.

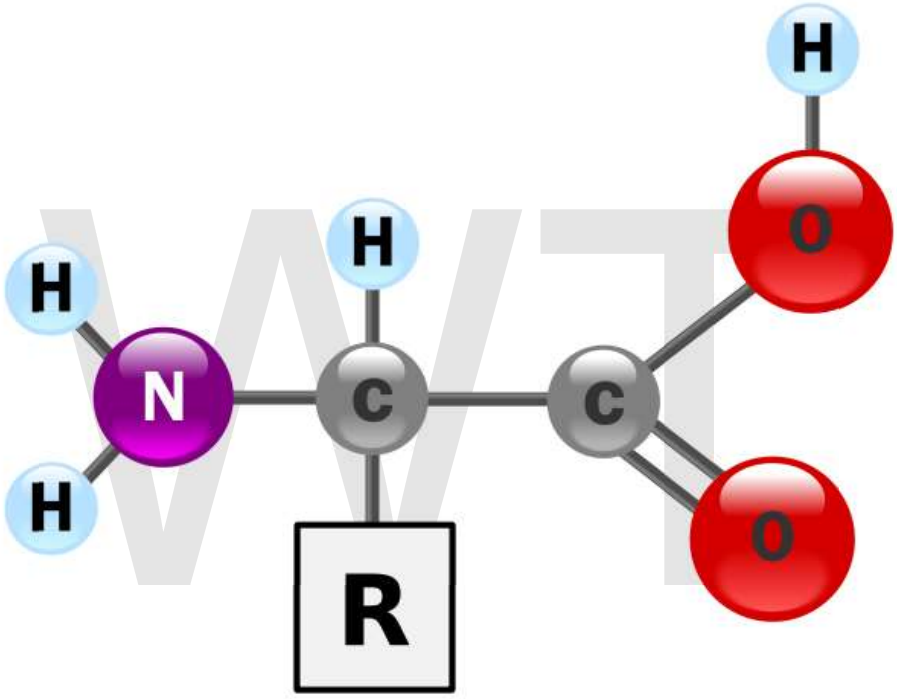
In animal nutrition

Taurine is an essential dietary requirement for feline health, since cats cannot synthesize the compound. The absence of taurine causes a cat's retina to slowly degenerate, causing eye problems and (eventually) irreversible blindness — a condition known as central retinal degeneration (CRD), as well as hair loss and tooth decay. Decreased plasma taurine concentration has been demonstrated to be associated with feline dilated cardiomyopathy. Unlike CRD, the condition is reversible with supplementation. Taurine is now a requirement of the Association of American Feed Control Officials (AAFCO) and any dry or wet food product labeled approved by the AAFCO should have a minimum of 0.1% taurine in dry food and 0.2% in wet food.

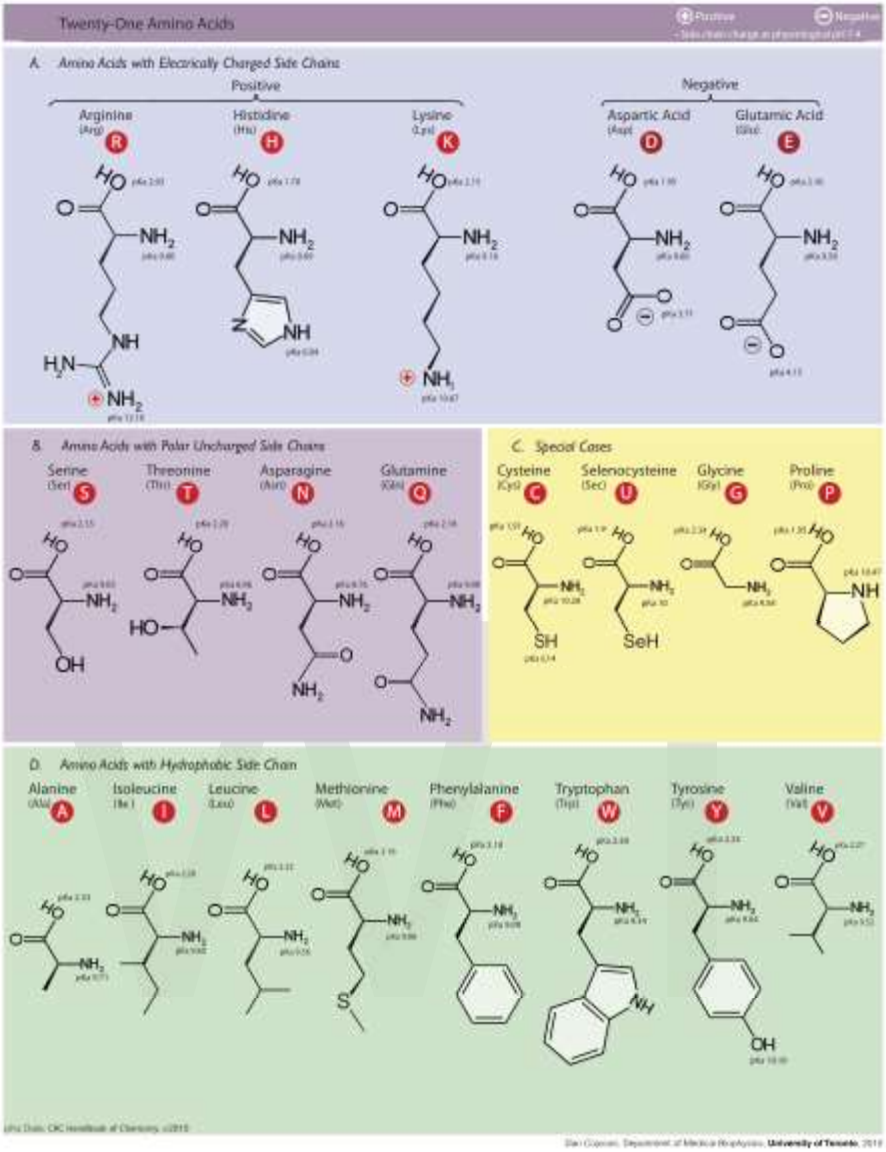
Research suggests that taurine is essential to the normal development of passerine birds. Many passerines seek out taurine-rich spiders to feed their young, particularly just after hatching. Researchers compared the behaviors and development of birds fed a taurine-supplemented diet to a control diet and found that juveniles that were fed taurine-rich diets as neonates were much larger risk takers and more adept at spatial learning tasks.

Chapter- 9

Amino Acid



The generic structure of an alpha amino acid in its unionized form



The 21 amino acids found in eukaryotes, grouped according to their side-chains' pKas and charge at physiological pH 7.4

Amino acids are molecules containing an amine group, a carboxylic acid group and a side-chain that varies between different amino acids. The key elements of an amino acid are carbon, hydrogen, oxygen, and nitrogen. They are particularly important in biochemistry, where the term usually refers to *alpha-amino acids*.

An alpha-amino acid has the generic formula $H_2NCHRCOOH$, where R is an organic substituent; the amino group is attached to the carbon atom immediately adjacent to the carboxylate group (the α–carbon). Other types of amino acid exist when the amino group is attached to a different carbon atom; for example, in gamma-amino acids (such as gamma-amino-butyric acid) the carbon atom to which the amino group attaches is

separated from the carboxylate group by two other carbon atoms. The various alpha-amino acids differ in which side-chain (R-group) is attached to their alpha carbon, and can vary in size from just one hydrogen atom in glycine to a large heterocyclic group in tryptophan.

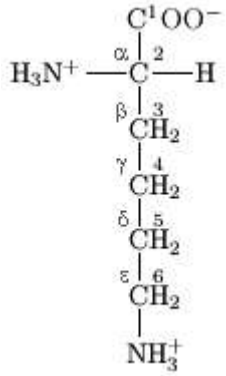
Amino acids are critical to life, and have many functions in metabolism. One particularly important function is to serve as the building blocks of proteins, which are linear chains of amino acids. Amino acids can be linked together in varying sequences to form a vast variety of proteins. Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids. Of these, 20 are encoded by the universal genetic code. Eight standard amino acids are called "essential" for humans because they cannot be created from other compounds by the human body, and so must be taken in as food.

Due to their central role in biochemistry, amino acids are important in nutrition and are commonly used in food technology and industry. In industry, applications include the production of biodegradable plastics, drugs, and chiral catalysts.

History

The first few amino acids were discovered in the early 19th century. In 1806, the French chemists Louis-Nicolas Vauquelin and Pierre Jean Robiquet isolated a compound in asparagus that proved to be asparagine, the first amino acid to be discovered. Another amino acid that was discovered in the early 19th century was cystine, in 1810, although its monomer, cysteine, was discovered much later, in 1884. Glycine and leucine were also discovered around this time, in 1820. Usage of the term *amino acid* in the English language is from 1898.

General structure



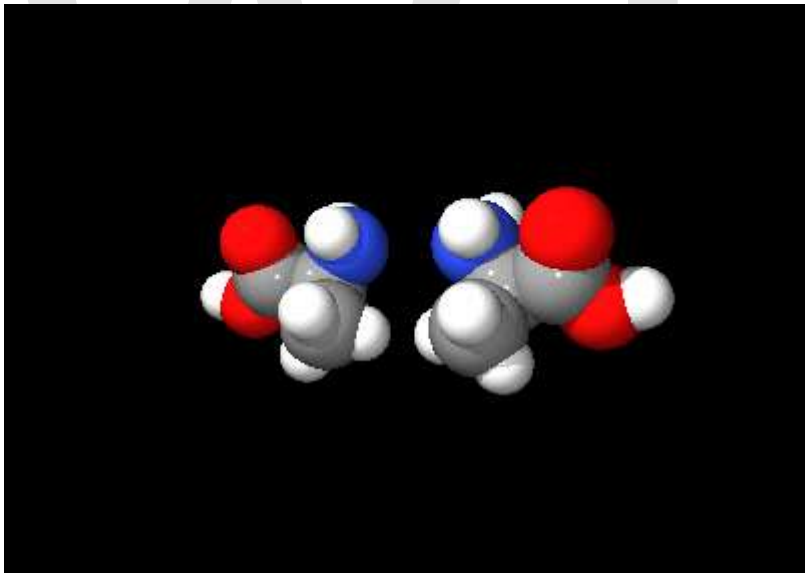
Lysine with the carbon atoms in the side-chain labeled

In the structure shown at the top of the page, **R** represents a side-chain specific to each amino acid. The carbon atom next to the carboxyl group is called the α–carbon and amino acids with a side-chain bonded to this carbon are referred to as *alpha amino acids*. These

are the most common form found in nature. In the alpha amino acids, the α–carbon is a chiral carbon atom, with the exception of glycine. In amino acids that have a carbon chain attached to the α–carbon (such as lysine, shown to the right) the carbons are labeled in order as α, β, γ, δ, and so on. In some amino acids, the amine group is attached to the β or γ-carbon, and these are therefore referred to as *beta* or *gamma amino acids*.

Amino acids are usually classified by the properties of their side-chain into four groups. The side-chain can make an amino acid a weak acid or a weak base, and a hydrophile if the side-chain is polar or a hydrophobe if it is nonpolar. The chemical structures of the 22 standard amino acids, along with their chemical properties, are described more fully in the article on these proteinogenic amino acids.

The phrase "branched-chain amino acids" or BCAA refers to the amino acids having aliphatic side-chains that are non-linear; these are leucine, isoleucine, and valine. Proline is the only proteinogenic amino acid whose side-group links to the α-amino group and, thus, is also the only proteinogenic amino acid containing a secondary amine at this position. In chemical terms, proline is, therefore, an imino acid, since it lacks a primary amino group, although it is still classed as an amino acid in the current biochemical nomenclature, and may also be called an "N-alkylated alpha-amino acid".

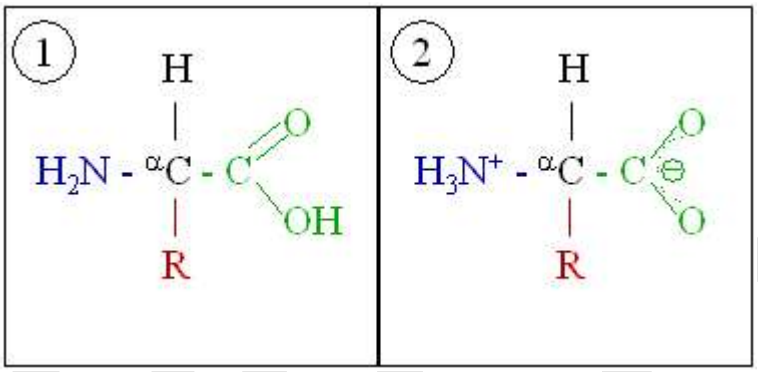


The two optical isomers of alanine, D-Alanine and L-Alanine

Isomerism

Of the standard α-amino acids, all but glycine can exist in either of two optical isomers, called L or D amino acids, which are mirror images of each other. While L-amino acids represent all of the amino acids found in proteins during translation in the ribosome, D-amino acids are found in some proteins produced by enzyme posttranslational modifications after translation and translocation to the endoplasmic reticulum, as in exotic sea-dwelling organisms such as cone snails. They are also abundant components of

the peptidoglycan cell walls of bacteria, and D-serine may act as a neurotransmitter in the brain. The L and D convention for amino acid configuration refers not to the optical activity of the amino acid itself, but rather to the optical activity of the isomer of glyceraldehyde from which that amino acid can, in theory, be synthesized (D-glyceraldehyde is dextrorotary; L-glyceraldehyde is levorotary). In alternative fashion, the *(S)* and *(R)* designators are used to indicate the absolute stereochemistry. Almost all of the amino acids in proteins are *(S)* at the α carbon, with cysteine being *(R)* and glycine non-chiral. Cysteine is unusual since it has a sulfur atom at the second position in its side-chain, which has a larger atomic mass than the groups attached to the first carbon, which is attached to the α-carbon in the other standard amino acids, thus the *(R)* instead of *(S)*.



An amino acid in its (1) unionized and (2) zwitterionic forms

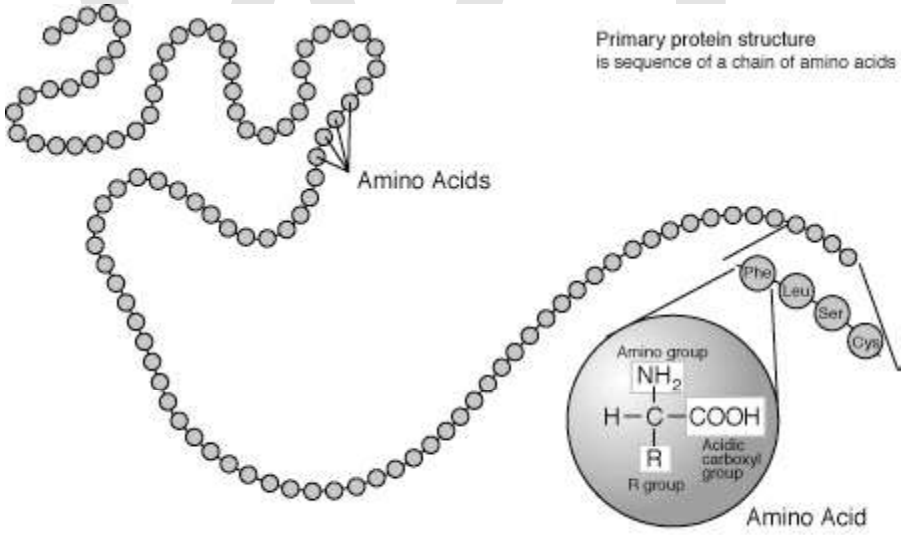
Zwitterions

The amine and carboxylic acid functional groups found in amino acids allow them to have amphiprotic properties. Carboxylic acid groups ($-CO_2H$) can be deprotonated to become negative carboxylates ($-CO_2^-$), and α-amino groups (NH_2-) can be protonated to become positive α-ammonium groups ($^+NH_3$-). At pH values greater than the pKa of the carboxylic acid group (mean for the 20 common amino acids is about 2.2), the negative carboxylate ion predominates. At pH values lower than the pKa of the α-ammonium group (mean for the 20 common α-amino acids is about 9.4), the nitrogen is predominantly protonated as a positively charged α-ammonium group. Thus, at pH between 2.2 and 9.4, the predominant form adopted by α-amino acids contains a negative carboxylate and a positive α-ammonium group, as shown in structure (2) on the right, so has net zero charge. This molecular state is known as a zwitterion, from the German **Zwitter** meaning *hermaphrodite* or *hybrid*. Below pH 2.2, the predominant form will have a neutral carboxylic acid group and a positive α-ammonium ion (net charge +1), and above pH 9.4, a negative carboxylate and neutral α-amino group (net charge -1). The fully neutral form (structure (1) on the right) is a very minor species in aqueous solution throughout the pH range (less than 1 part in 10^7). Amino acids also exist as zwitterions in the solid phase, and crystallize with salt-like properties unlike typical organic acids or amines.

Isoelectric point

At pH values between the two pKa values, the zwitterion predominates, but coexists in dynamic equilibrium with small amounts of net negative and net positive ions. At the exact midpoint between the two pKa values, the trace amount of net negative and trace of net positive ions exactly balance, so that average net charge of all forms present is zero. This pH is known as the isoelectric point pI, so $pI = ½(pKa_1 + pKa_2)$. The individual amino acids all have slightly different pKa values, so have different isoelectric points. For amino acids with charged side-chains, the pKa of the side-chain is involved. Thus for Asp, Glu with negative side-chains, $pI = ½(pKa_1 + pKa_R)$, where pKa_R is the side-chain pKa. Cysteine also has potentially negative side-chain with $pKa_R = 8.14$, so pI should be calculated as for Asp and Glu, even though the side-chain is not significantly charged at neutral pH. For His, Lys, and Arg with positive side-chains, $pI = ½(pKa_R + pKa_2)$. Amino acids have zero mobility in electrophoresis at their isoelectric point, although this behaviour is more usually exploited for peptides and proteins than single amino acids. Zwitterions have minimum solubility at their isolectric point and some amino acids (in particular, with non-polar side-chains) can be isolated by precipitation from water by adjusting the pH to the required isoelectric point.

Occurrence and functions in biochemistry



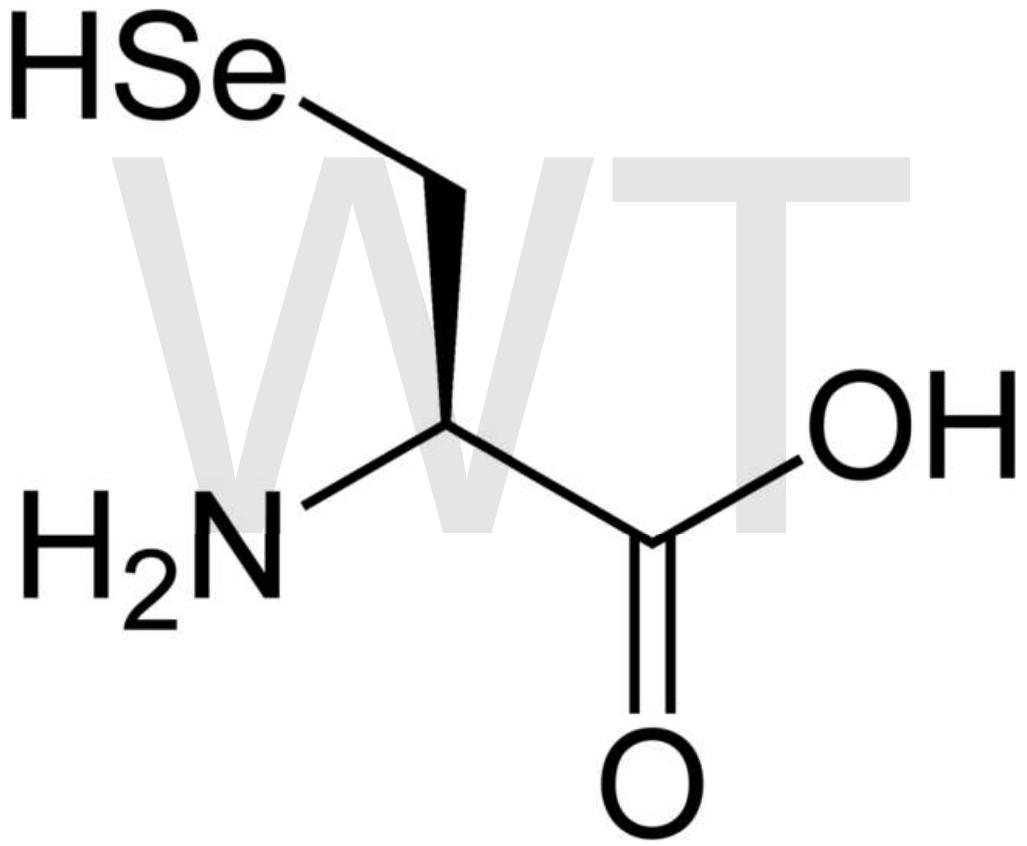
A polypeptide is an unbranched chain of amino acids

Standard amino acids

Amino acids are the structural units that make up proteins. They join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighboring amino acids. The process of making proteins is called *translation* and involves the step-by-step addition of amino acids to a growing protein chain by a ribozyme that is called a ribosome. The order in which the amino acids are

added is read through the genetic code from an mRNA template, which is a RNA copy of one of the organism's genes.

Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids. Of these, 20 are encoded by the universal genetic code. The remaining 2, selenocysteine and pyrrolysine, are incorporated into proteins by unique synthetic mechanisms. Selenocysteine is incorporated when the mRNA being translated includes a SECIS element, which causes the UGA codon to encode selenocysteine instead of a stop codon. Pyrrolysine is used by some methanogenic archaea in enzymes that they use to produce methane. It is coded for with the codon UAG, which is normally a stop codon in other organisms.

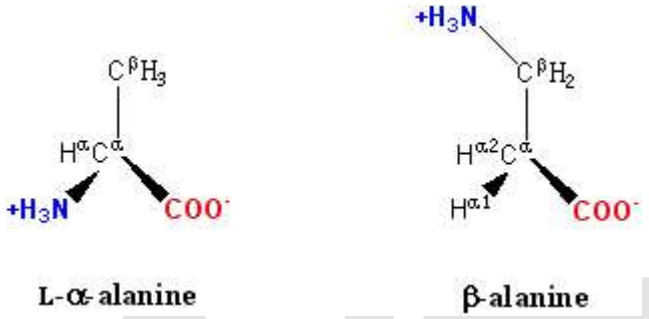


The amino acid selenocysteine

Non-standard amino acids

Aside from the 22 standard amino acids, there are many other amino acids that are called *non-proteinogenic* or *non-standard*. Those either are not found in proteins (for example carnitine, GABA, and L-DOPA), or are not produced directly and in isolation by standard cellular machinery (for example, hydroxyproline and selenomethionine).

Non-standard amino acids that are found in proteins are formed by post-translational modification, which is modification after translation during protein synthesis. These modifications are often essential for the function or regulation of a protein; for example, the carboxylation of glutamate allows for better binding of calcium cations, and the hydroxylation of proline is critical for maintaining connective tissues. Another example is the formation of hypusine in the translation initiation factor EIF5A, through modification of a lysine residue. Such modifications can also determine the localization of the protein, e.g., the addition of long hydrophobic groups can cause a protein to bind to a phospholipid membrane.



β-alanine and its α-alanine isomer

Some nonstandard amino acids are not found in proteins. Examples include lanthionine, 2-aminoisobutyric acid, dehydroalanine, and the neurotransmitter gamma-aminobutyric acid. Nonstandard amino acids often occur as intermediates in the metabolic pathways for standard amino acids — for example, ornithine and citrulline occur in the urea cycle, part of amino acid catabolism (see below). A rare exception to the dominance of α-amino acids in biology is the β-amino acid beta alanine (3-aminopropanoic acid), which is used in plants and microorganisms in the synthesis of pantothenic acid (vitamin B_5), a component of coenzyme A.

In human nutrition

When taken up into the human body from the diet, the 22 standard amino acids either are used to synthesize proteins and other biomolecules or are oxidized to urea and carbon dioxide as a source of energy. The oxidation pathway starts with the removal of the amino group by a transaminase, the amino group is then fed into the urea cycle. The other product of transamidation is a keto acid that enters the citric acid cycle. Glucogenic amino acids can also be converted into glucose, through gluconeogenesis.

Pyrrolysine trait is restricted to several microbes, and only one organism has both Pyl and Sec. Of the 22 standard amino acids, 8 are called essential amino acids because the human body cannot synthesize them from other compounds at the level needed for normal growth, so they must be obtained from food. In addition, cysteine, taurine, tyrosine, histidine, and arginine are semiessential amino-acids in children, because the metabolic pathways that synthesize these amino acids are not fully developed. The

amounts required also depend on the age and health of the individual, so it is hard to make general statements about the dietary requirement for some amino acids.

Essential	Nonessential
Isoleucine	Alanine
Leucine	Asparagine
Lysine	Aspartic Acid
Methionine	Cysteine*
Phenylalanine	Glutamic Acid
Threonine	Glutamine*
Tryptophan	Glycine*
Valine	Proline*
	Selenocysteine*
	Serine*
	Tyrosine*
	Arginine*
	Histidine*
	Ornithine*
	Taurine*

(*) Essential only in certain cases.

Non-protein functions

In humans, non-protein amino acids also have important roles as metabolic intermediates, such as in the biosynthesis of the neurotransmitter gamma-aminobutyric acid. Many amino acids are used to synthesize other molecules, for example:

- Tryptophan is a precursor of the neurotransmitter serotonin.
- Tyrosine is a precursor of the neurotransmitter dopamine.
- Glycine is a precursor of porphyrins such as heme.
- Arginine is a precursor of nitric oxide.
- Ornithine and S-adenosylmethionine are precursors of polyamines.
- Aspartate, glycine, and glutamine are precursors of nucleotides.
- Phenylalanine is a precursor of various phenylpropanoids, which are important in plant metabolism.

However, not all of the functions of other abundant non-standard amino acids are known. For example, taurine is a major amino acid in muscle and brain tissues, but, although many functions have been proposed, its precise role in the body has not been determined.

Some non-standard amino acids are used as defenses against herbivores in plants. For example canavanine is an analogue of arginine that is found in many legumes, and in

particularly large amounts in *Canavalia gladiata* (sword bean). This amino acid protects the plants from predators such as insects and can cause illness in people if some types of legumes are eaten without processing. The non-protein amino acid mimosine is found in other species of legume, particularly *Leucaena leucocephala*. This compound is an analogue of tyrosine and can poison animals that graze on these plants.

Uses in technology

Amino acids are used for a variety of applications in industry, but their main use is as additives to animal feed. This is necessary, since many of the bulk components of these feeds, such as soybeans, either have low levels or lack some of the essential amino acids: Lysine, methionine, threonine, and tryptophan are most important in the production of these feeds. The food industry is also a major consumer of amino acids, in particular, glutamic acid, which is used as a flavor enhancer, and Aspartame (aspartyl-phenylalanine-1-methyl ester) as a low-calorie artificial sweetener. The remaining production of amino acids is used in the synthesis of drugs and cosmetics.

Amino acid derivative	Pharmaceutical application
5-HTP (5-hydroxytryptophan)	Experimental treatment for depression.
L-DOPA (L-dihydroxyphenylalanine)	Treatment for Parkinsonism.
Eflornithine	Drug that inhibits ornithine decarboxylase and is used in the treatment of sleeping sickness.

Expanded genetic code

Since 2001, 40 non-natural amino acids have been added into protein by creating a unique codon (recoding) and a corresponding transfer-RNA:aminoacyl – tRNA-synthetase pair to encode it with diverse physicochemical and biological properties in order to be used as a tool to exploring protein structure and function or to create novel or enhanced proteins.

Chemical building blocks

Amino acids are important as low-cost feedstocks. These compounds are used in chiral pool synthesis as enantiomerically-pure building blocks.

Amino acids have been investigated as precursors chiral catalysts, e.g., for asymmetric hydrogenation reactions, although no commercial applications exist.

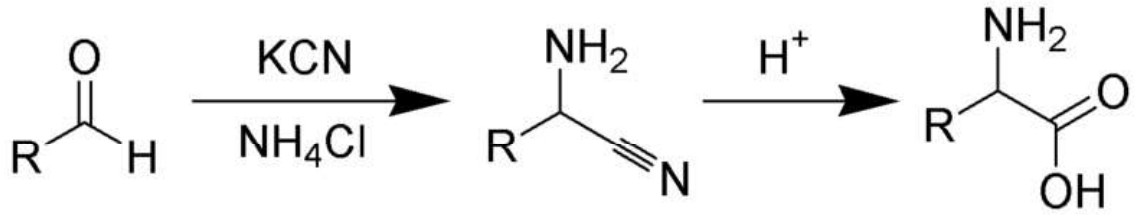
Biodegradable plastics

Amino acids are under development as components of a range of biodegradable polymers. These materials have applications as environmentally-friendly packaging and in medicine in drug delivery and the construction of prosthetic implants. These polymers

include polypeptides, polyamides, polyesters, polysulfides, and polyurethanes with amino acids either forming part of their main chains or bonded as side-chains. These modifications alter the physical properties and reactivities of the polymers. An interesting example of such materials is polyaspartate, a water-soluble biodegradable polymer that may have applications in disposable diapers and agriculture. Due to its solubility and ability to chelate metal ions, polyaspartate is also being used as a biodegradeable anti-scaling agent and a corrosion inhibitor. In addition, the aromatic amino acid tyrosine is being developed as a possible replacement for toxic phenols such as bisphenol A in the manufacture of polycarbonates.

Reactions

As amino acids have both a primary amine group and a primary carboxyl group, these chemicals can undergo most of the reactions associated with these functional groups. These include nucleophilic addition, amide bond formation and imine formation for the amine group and esterification, amide bond formation and decarboxylation for the carboxylic acid group. The multiple side-chains of amino acids can also undergo chemical reactions. The types of these reactions are determined by the groups on these side-chains and are, therefore, different between the various types of amino acid.



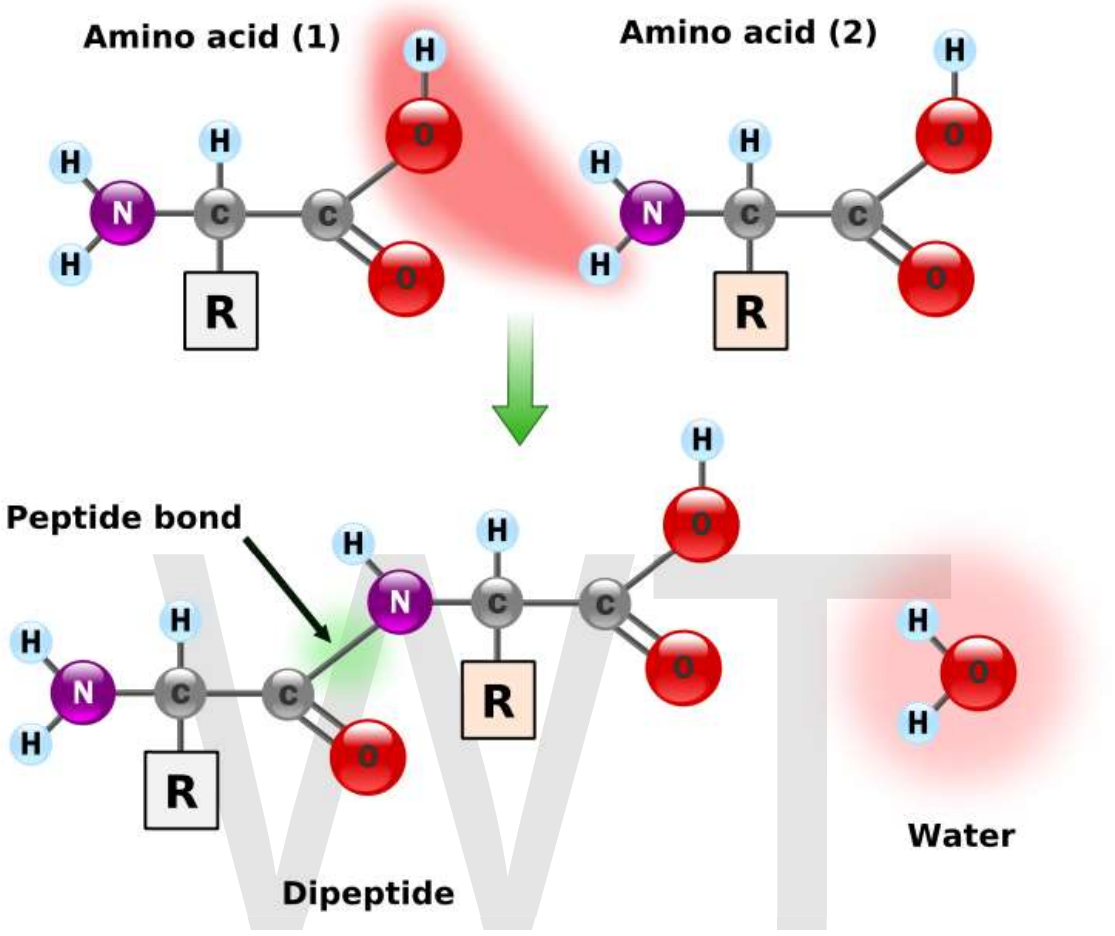
The Strecker amino acid synthesis

Chemical synthesis

Several methods exist to synthesize amino acids. One of the oldest methods begins with the bromination at the α-carbon of a carboxyic acid. Nucleophilic substitution with ammonia then converts the alkyl bromide to the amino acid. In alternative fashion, the Strecker amino acid synthesis involves the treatment of an aldehyde with potassium cyanide and ammonia, this produces an α-amino nitrile as an intermediate. Hydrolysis of the nitrile in acid then yields a α-amino acid. Using ammonia or ammonium salts in this reaction gives unsubstituted amino acids, while substituting primary and secondary amines will yield substituted amino acids. Likewise, using ketones, instead of aldehydes, gives α,α-disubstituted amino acids. The classical synthesis gives racemic mixtures of α-amino acids as products, but several alternative procedures using asymmetric auxiliaries or asymmetric catalysts have been developed.

At the current time, the most-adopted method is an automated synthesis on a solid support (e.g., polystyrene beads), using protecting groups (e.g., Fmoc and t-Boc) and activating groups (e.g., DCC and DIC).

Peptide bond formation



The condensation of two amino acids to form a peptide bond

As both the amine and carboxylic acid groups of amino acids can react to form amide bonds, one amino acid molecule can react with another and become joined through an amide linkage. This polymerization of amino acids is what creates proteins. This condensation reaction yields the newly formed peptide bond and a molecule of water. In cells, this reaction does not occur directly; instead the amino acid is first activated by attachment to a transfer RNA molecule through an ester bond. This aminoacyl-tRNA is produced in an ATP-dependent reaction carried out by an aminoacyl tRNA synthetase. This aminoacyl-tRNA is then a substrate for the ribosome, which catalyzes the attack of the amino group of the elongating protein chain on the ester bond. As a result of this mechanism, all proteins made by ribosomes are synthesized starting at their N-terminus and moving towards their C-terminus.

However, not all peptide bonds are formed in this way. In a few cases, peptides are synthesized by specific enzymes. For example, the tripeptide glutathione is an essential part of the defenses of cells against oxidative stress. This peptide is synthesized in two steps from free amino acids. In the first step gamma-glutamylcysteine synthetase

condenses cysteine and glutamic acid through a peptide bond formed between the side-chain carboxyl of the glutamate (the gamma carbon of this side-chain) and the amino group of the cysteine. This dipeptide is then condensed with glycine by glutathione synthetase to form glutathione.

In chemistry, peptides are synthesized by a variety of reactions. One of the most-used in solid-phase peptide synthesis uses the aromatic oxime derivatives of amino acids as activated units. These are added in sequence onto the growing peptide chain, which is attached to a solid resin support. The ability to easily synthesize vast numbers of different peptides by varying the types and order of amino acids (using combinatorial chemistry) has made peptide synthesis particularly important in creating libraries of peptides for use in drug discovery through high-throughput screening.

Biosynthesis and catabolism

In plants, nitrogen is first assimilated into organic compounds in the form of glutamate, formed from alpha-ketoglutarate and ammonia in the mitochondrion. In order to form other amino acids, the plant uses transaminases to move the amino group to another alpha-keto carboxylic acid. For example, aspartate aminotransferase converts glutamate and oxaloacetate to alpha-ketoglutarate and aspartate. Other organisms use transaminases for amino acid synthesis, too. Transaminases are also involved in breaking down amino acids. Degrading an amino acid often involves moving its amino group to alpha-ketoglutarate, forming glutamate. In many vertebrates, the amino group is then removed through the urea cycle and is excreted in the form of urea. However, amino acid degradation can produce uric acid or ammonia instead. For example, serine dehydratase converts serine to pyruvate and ammonia.

Nonstandard amino acids are usually formed through modifications to standard amino acids. For example, homocysteine is formed through the transsulfuration pathway or by the demethylation of methionine via the intermediate metabolite S-adenosyl methionine, while hydroxyproline is made by a posttranslational modification of proline.

Microorganisms and plants can synthesize many uncommon amino acids. For example, some microbes make 2-aminoisobutyric acid and lanthionine, which is a sulfide-bridged derivative of alanine. Both of these amino acids are found in peptidic lantibiotics such as alamethicin. While in plants, 1-aminocyclopropane-1-carboxylic acid is a small disubstituted cyclic amino acid that is a key intermediate in the production of the plant hormone ethylene.

Physicochemical properties of amino acids

The 20 amino acids encoded directly by the genetic code can be divided into several groups based on their properties. Important factors are charge, hydrophilicity or hydrophobicity, size, and functional groups. These properties are important for protein structure and protein–protein interactions. The water-soluble proteins tend to have their hydrophobic residues (Leu, Ile, Val, Phe, and Trp) buried in the middle of the protein,

whereas hydrophilic side-chains are exposed to the aqueous solvent. The integral membrane proteins tend to have outer rings of exposed hydrophobic amino acids that anchor them into the lipid bilayer. In the case part-way between these two extremes, some peripheral membrane proteins have a patch of hydrophobic amino acids on their surface that locks onto the membrane. In similar fashion, proteins that have to bind to positively-charged molecules have surfaces rich with negatively charged amino acids like glutamate and aspartate, while proteins binding to negatively-charged molecules have surfaces rich with positively charged chains like lysine and arginine. There are different hydrophobicity scales of amino acid residues.

Some amino acids have special properties such as cysteine, that can form covalent disulfide bonds to other cysteine residues, proline that forms a cycle to the polypeptide backbone, and glycine that is more flexible than other amino acids.

Many proteins undergo a range of posttranslational modifications, when additional chemical groups are attached to the amino acids in proteins. Some modifications can produce hydrophobic lipoproteins, or hydrophilic glycoproteins. These type of modification allow the reversible targeting of a protein to a membrane. For example, the addition and removal of the fatty acid palmitic acid to cysteine residues in some signaling proteins causes the proteins to attach and then detach from cell membranes.

Table of standard amino acid abbreviations and properties

Amino Acid	3-Letter	1-Letter	Side-chain polarity	Side-chain charge (pH 7.4)	Hydropathy index	Absorbance λ_{max}(nm)	ε at λ_{max} ($\times 10^{-3}$ M^{-1} cm^{-1})
Alanine	Ala	A	nonpolar	neutral	1.8		
Arginine	Arg	R	polar	positive	−4.5		
Asparagine	Asn	N	polar	neutral	−3.5		
Aspartic acid	Asp	D	polar	negative	−3.5		
Cysteine	Cys	C	nonpolar	neutral	2.5	250	0.3
Glutamic acid	Glu	E	polar	negative	−3.5		
Glutamine	Gln	Q	polar	neutral	−3.5		
Glycine	Gly	G	nonpolar	neutral	−0.4		
Histidine	His	H	polar	positive(10%) neutral(90%)	−3.2	211	5.9
Isoleucine	Ile	I	nonpolar	neutral	4.5		
Leucine	Leu	L	nonpolar	neutral	3.8		
Lysine	Lys	K	polar	positive	−3.9		
Methionine	Met	M	nonpolar	neutral	1.9		

Phenylalanine	Phe	F	nonpolar	neutral	2.8	257, 206, 188	0.2, 9.3, 60.0
Proline	Pro	P	nonpolar	neutral	−1.6		
Serine	Ser	S	polar	neutral	−0.8		
Threonine	Thr	T	polar	neutral	−0.7		
Tryptophan	Trp	W	nonpolar	neutral	−0.9	280, 219	5.6, 47.0
Tyrosine	Tyr	Y	polar	neutral	−1.3	274, 222, 193	1.4, 8.0, 48.0
Valine	Val	V	nonpolar	neutral	4.2		

In addition, there are two additional amino acids that are incorporated by overriding stop codons:

21st and 22nd amino acids	**3-Letter**	**1-Letter**
Selenocysteine	Sec	U
Pyrrolysine	Pyl	O

In addition to the specific amino acid codes, placeholders are used in cases where chemical or crystallographic analysis of a peptide or protein cannot conclusively determine the identity of a residue.

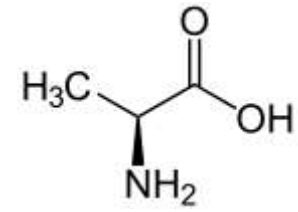
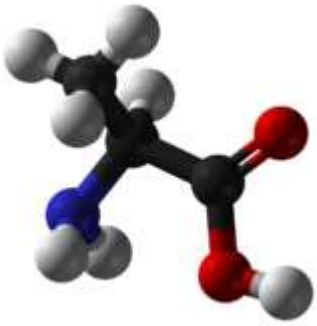
Ambiguous Amino Acids	**3-Letter**	**1-Letter**
Asparagine or aspartic acid	Asx	B
Glutamine or glutamic acid	Glx	Z
Leucine or Isoleucine	Xle	J
Unspecified or unknown amino acid	Xaa	X

Unk is sometimes used instead of **Xaa**, but is less standard.

In addition, many non-standard amino acids have a specific code. For example, several peptide drugs, such as Bortezomib and MG132, are artificially synthesized and retain their protecting groups, which have specific codes. Bortezomib is Pyz-Phe-boroLeu, and MG132 is Z-Leu-Leu-Leu-al. To aid in the analysis of protein structure, photocrosslinking amino acid analogues are available. These include photoleucine (**pLeu**) and photomethionine (**pMet**).

Chapter- 10

Alanine

Alanine	
 	
IUPAC name Alanine **Other names** 2-Aminopropanoic acid	
Identifiers	
CAS number	338-69-2 (D-isomer)✓, 56-41-7 (L-isomer), 302-72-7 (racemic)
PubChem	5950
ChemSpider	64234 (D-isomer)✓, 5735 (L-isomer), 582 (Racemic)
UNII	1FU7983T0U✓
EC-number	206-126-4
KEGG	C01401✗
ChEMBL	CHEMBL66693✗
IUPHAR ligand	720
Properties	
Molecular formula	$C_3H_7NO_2$
Molar mass	89.09 g mol^{-1}
Appearance	white powder

Density	1.424 g/cm^3
Melting point	258 ºC subl.
Solubility in water	soluble
Acidity (pK_a)	2.35 (carboxyl), 9.69 (amino)

Supplementary data page

Structure and properties	n, ε_r, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

Alanine (abbreviated as **Ala** or **A**) is an α-amino acid with the chemical formula $CH_3CH(NH_2)COOH$. The L-isomer is one of the 22 proteinogenic amino acids, i.e., the building blocks of proteins. Its codons are GCU, GCC, GCA, and GCG. It is classified as a nonpolar amino acid. L-Alanine is second only to leucine in rate of occurrence, accounting for 7.8% of the primary structure in a sample of 1,150 proteins. D-Alanine occurs in bacterial cell walls and in some peptide antibiotics.

Structure

The α-carbon atom of alanine is bound with a methyl group ($-CH_3$), making it one of the simplest α-amino acids with respect to molecular structure and also resulting in alanine's being classified as an aliphatic amino acid. The methyl group of alanine is non-reactive and is thus almost never directly involved in protein function.

Sources

Dietary sources

Alanine is a nonessential amino acid, meaning it can be manufactured by the human body, and does not need to be obtained directly through the diet. Alanine is found in a wide variety of foods, but is particularly concentrated in meats.

Good sources of alanine include

- **Animal sources**: meat, seafood, caseinate, dairy products, eggs, fish, gelatin, lactalbumin
- **Vegetarian sources**: beans, nuts, seeds, soy, whey, brewer's yeast, brown rice, bran, corn, legumes, whole grains.

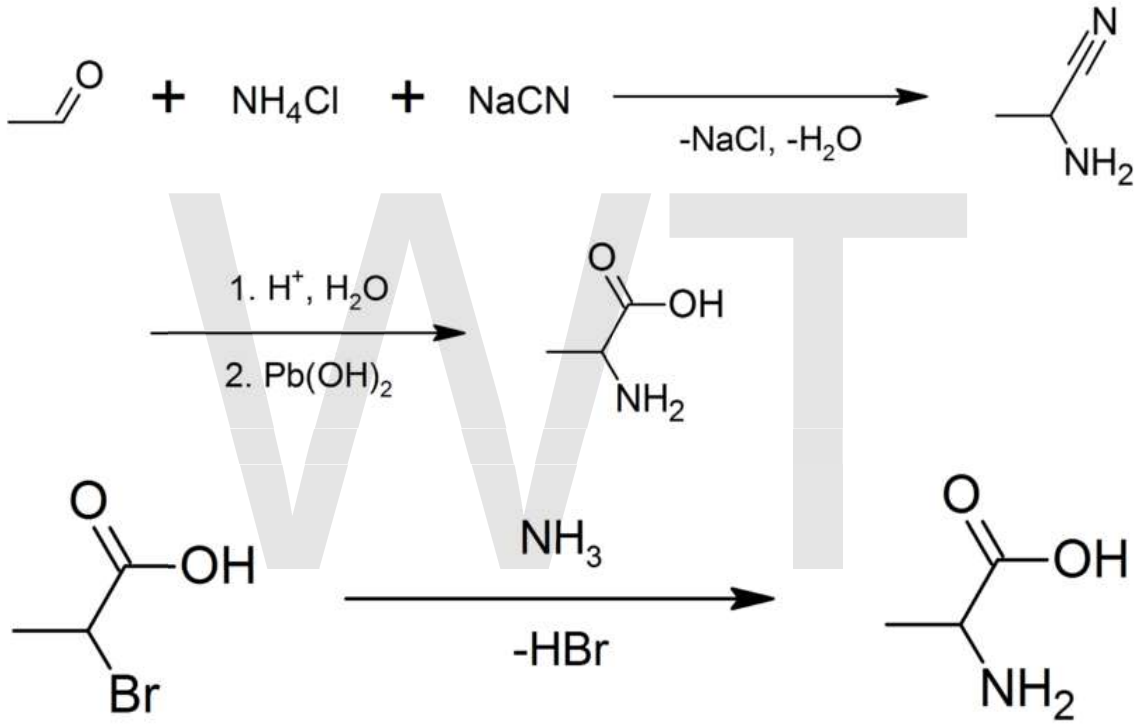
Biosynthesis

Alanine can be manufactured in the body from pyruvate and branched chain amino acids such as valine, leucine, and isoleucine.

Alanine is most commonly produced by reductive amination of pyruvate. Because transamination reactions are readily reversible and pyruvate pervasive, alanine can be easily formed and thus has close links to metabolic pathways such as glycolysis, gluconeogenesis, and the citric acid cycle. It also arises together with lactate and generates glucose from protein via the alanine cycle.

Chemical synthesis

Racemic alanine can be prepared by the condensation of acetaldehyde with ammonium chloride in the presence of sodium cyanide by the Strecker reaction, or by the ammonolysis of 2-bromopropionic acid:



Physiological function

Glucose–alanine cycle

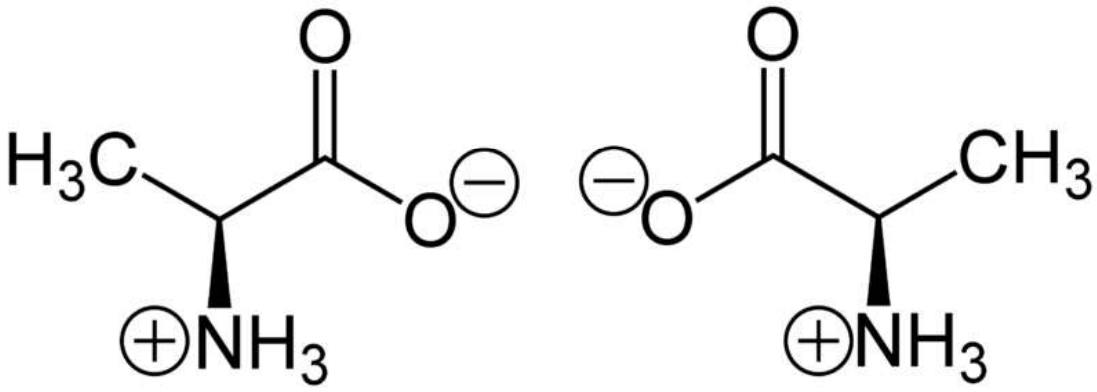
Alanine plays a key role in glucose–alanine cycle between tissues and liver. In muscle and other tissues that degrade amino acids for fuel, amino groups are collected in the form of glutamate by transamination. Glutamate can then transfer its amino group through the action of alanine aminotransferase to pyruvate, a product of muscle glycolysis, forming alanine and α-ketoglutarate. The alanine formed is passed into the blood and transported to the liver. A reverse of the alanine aminotransferase reaction takes place in liver. Pyruvate regenerated forms glucose through gluconeogenesis, which returns to muscle through the circulation system. Glutamate in the liver enters

mitochondria and degrades into ammonium ion through the action of glutamate dehydrogenase, which in turn participate in the urea cycle to form urea.

The glucose–alanine cycle enables pyruvate and glutamate to be removed from the muscle and find their way to the liver. Glucose is regenerated from pyruvate and then returned to muscle: the energetic burden of gluconeogenesis is thus imposed on the liver instead of the muscle. All available ATP in muscle is devoted to muscle contraction.

Link to hypertension

An international study led by Imperial College London found a correlation between high levels of alanine and higher blood pressure, energy intake, cholesterol levels, and body mass index.



(*S*)-Alanine (left) and (*R*)-alanine (right) in zwitterionic form at neutral pH

Chemical properties

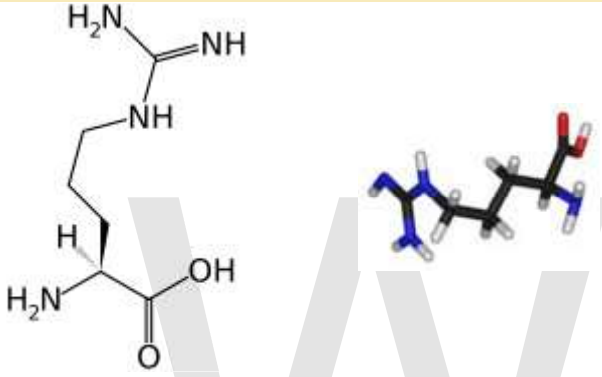
Free radical stability

The deamination of an alanine molecule produces a stable alkyl free radical, $CH_3C^{\bullet}HCOO^-$. Deamination can be induced in solid or aqueous alanine by radiation.

This property of alanine is used in dosimetric measurements in radiotherapy. When normal alanine is irradiated, the radiation causes certain alanine molecules to become free radicals, and, as these radicals are stable, the free radical content can later be measured in order to find out how much radiation the alanine was exposed to. In this way, one can be assured that complex radiotherapy treatment plans will deliver the intended pattern of radiation dose.

Chapter- 11

Arginine

L-Arginine	
	
IUPAC name (*S*)-2-Amino-5-guanidinopentanoic acid	
Other names Arginine	
Identifiers	
CAS number	74-79-3 ✓
PubChem	6322
ChemSpider	227 ✓
UNII	94ZLA3W45F ✓
KEGG	C02385 ✓
ChEMBL	CHEMBL179653 ✓
IUPHAR ligand	721
Properties	
Molecular formula	$C_6H_{14}N_4O_2$
Molar mass	174.2 g mol^{-1}
Supplementary data page	
Structure and properties	*n*, ε_r, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

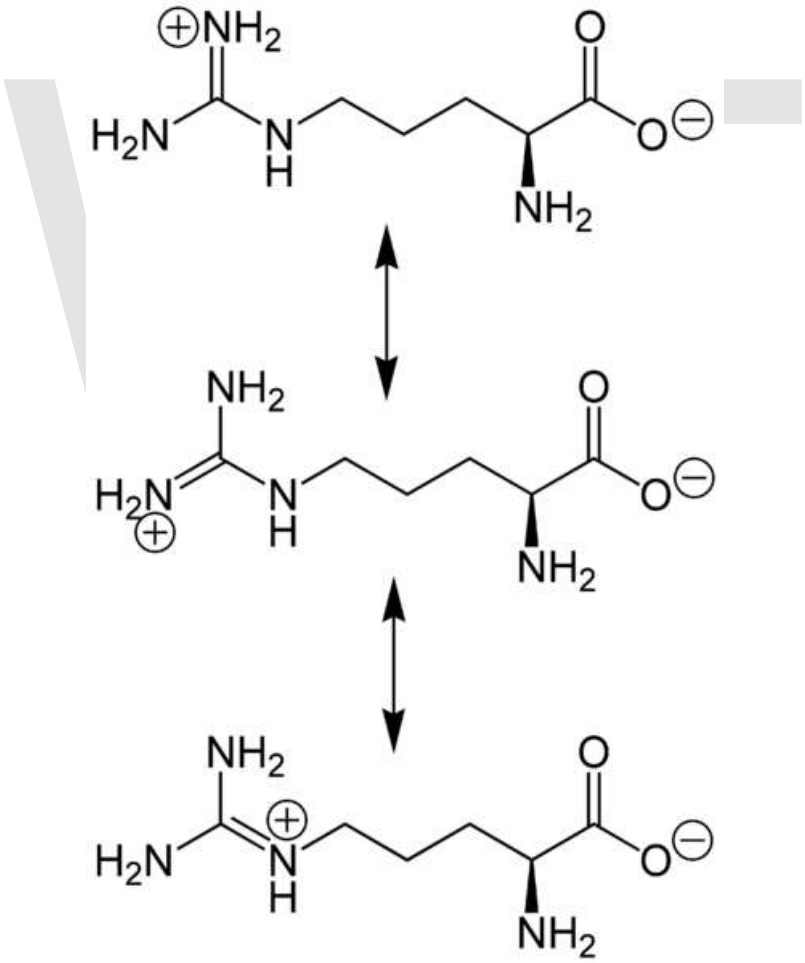
Arginine (abbreviated as **Arg** or **R**) is an α-amino acid. The L-form is one of the 20 most common natural amino acids. At the level of molecular genetics, in the structure of the messenger ribonucleic acid mRNA, CGU, CGC, CGA, CGG, AGA, and AGG, are the

triplets of nucleotide bases or codons that codify for arginine during protein synthesis. In mammals, arginine is classified as a semiessential or conditionally essential amino acid, depending on the developmental stage and health status of the individual. Preterm infants are unable synthesize or create arginine internally, making the amino acid nutritionally essential for them. Arginine was first isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze.

In general, most people do not need to take arginine supplements because the body usually produces enough.

Structure

The amino acid side chain of arginine consists of a 3-carbon aliphatic straight chain, the distal end of which is capped by a complex guanidinium group.



Delocalization of charge in guanidinium group of L-Arginine

With a pK_a of 12.48, the guanidinium group is positively charged in neutral, acidic and even most basic environments, and thus imparts basic chemical properties to arginine.

Because of the conjugation between the double bond and the nitrogen lone pairs, the positive charge is delocalized, enabling the formation of multiple H-bonds.

Sources

Dietary sources

Arginine is a conditionally nonessential amino acid, meaning most of the time it can be manufactured by the human body, and does not need to be obtained directly through the diet. The biosynthetic pathway however does not produce sufficient arginine, and some must still be consumed through diet. Individuals who have poor nutrition or certain physical conditions may be advised to increase their intake of foods containing arginine. Arginine is found in a wide variety of foods, including:

- Animal sources

  dairy products (e.g. cottage cheese, ricotta, milk, yogurt, whey protein drinks), beef, pork (e.g. bacon, ham), gelatin, poultry (e.g. chicken and turkey light meat), wild game (e.g. pheasant, quail), seafood (e.g. halibut, lobster, salmon, shrimp, snails, tuna)

- Plant sources

  wheat germ and flour, buckwheat, granola, oatmeal, peanuts, nuts (coconut, pecans, cashews, walnuts, almonds, Brazil nuts, hazelnuts, pinenuts), seeds (pumpkin, sesame, sunflower), chick peas, cooked soybeans, *Phalaris canariensis* (canaryseed or ALPISTE)

Biosynthesis

Arginine is synthesized from citrulline by the sequential action of the cytosolic enzymes argininosuccinate synthetase (ASS) and argininosuccinate lyase (ASL). This is energetically costly, as the synthesis of each molecule of argininosuccinate requires hydrolysis of adenosine triphosphate (ATP) to adenosine monophosphate (AMP); *i.e.*, two ATP equivalents.

Citrulline can be derived from multiple sources:

- from arginine via nitric oxide synthase (NOS)
- from ornithine via catabolism of proline or glutamine/glutamate
- from asymmetric dimethylarginine (ADMA) via DDAH

The pathways linking arginine, glutamine, and proline are bidirectional. Thus, the net utilization or production of these amino acids is highly dependent on cell type and developmental stage.

On a whole-body basis, synthesis of arginine occurs principally via the intestinal–renal axis, wherein epithelial cells of the small intestine, which produce citrulline primarily from glutamine and glutamate, collaborate with the proximal tubule cells of the kidney, which extract citrulline from the circulation and convert it to arginine, which is returned to the circulation. Consequently, impairment of small bowel or renal function can reduce endogenous arginine synthesis, thereby increasing the dietary requirement.

Synthesis of arginine from citrulline also occurs at a low level in many other cells, and cellular capacity for arginine synthesis can be markedly increased under circumstances that also induce iNOS. Thus, citrulline, a coproduct of the NOS-catalyzed reaction, can be recycled to arginine in a pathway known as the citrulline-NO or arginine-citrulline pathway. This is demonstrated by the fact that in many cell types, citrulline can substitute for arginine to some degree in supporting NO synthesis. However, recycling is not quantitative because citrulline accumulates along with nitrate and nitrite, the stable end-products of NO, in NO-producing cells.

Function

Arginine plays an important role in cell division, the healing of wounds, removing ammonia from the body, immune function, and the release of hormones. Arginine taken in combination with proanthocyanidins or yohimbine, has also been used as a treatment for erectile dysfunction.

The benefits and functions attributed to oral supplementation of L-arginine include:

- Precursor for the synthesis of nitric oxide (NO)
- Reduces healing time of injuries (particularly bone)
- Quickens repair time of damaged tissue
- Helps decrease blood pressure

Proteins

The distributing basics of the moderate structure found in geometry, charge distribution and ability to form multiple H-bonds make arginine ideal for binding negatively charged groups. For this reason, arginine prefers to be on the outside of the proteins where it can interact with the polar environment.

Incorporated in proteins, arginine can also be converted to citrulline by PAD enzymes. In addition, arginine can be methylated by protein methyltransferases.

Precursor

Arginine is the immediate precursor of NO, urea, ornithine and agmatine; is necessary for the synthesis of creatine; and can also be used for the synthesis of polyamines (mainly through ornithine and to a lesser degree through agmatine), citrulline, and glutamate. As a precursor of nitric oxide, arginine may have a role in the treatment of some conditions

where vasodilation is required. The presence of asymmetric dimethylarginine (ADMA), a close relative, inhibits the nitric oxide reaction; therefore, ADMA is considered a marker for vascular disease, just as L-arginine is considered a sign of a healthy endothelium.

Treatment of herpes simplex virus

An unproven claim is that a low ratio of arginine to lysine may be of benefit in the treatment of herpes simplex virus. For more information, refer to Herpes - Treatment.

Possible increased risk of death after supplementation following heart attack

A clinical trial found that patients taking an L-arginine supplement following a heart attack found no change in the heart's vascular tone or decrease in the symptoms of congestive heart failure (the hearts' ability to pump). In fact, six more patients who were taking L-arginine died than those taking a placebo resulting in early termination of the study with the recommendation that the supplement not be used by heart attack patients. Despite these findings, the supplement is still widely marketed as beneficial for the heart.

Potential medical uses

Lung inflammation and asthma

The Mayo Clinic web page on L-arginine reports that inhalation of L-arginine can increase lung inflammation and worsen asthma.

Growth hormone

Arginine may stimulate the secretion of growth hormone, and is used in growth hormone stimulation tests.

MELAS syndrome

Several trials delved into effects of L-arginine in MELAS syndrome, a mitochondrial disease.

Sepsis

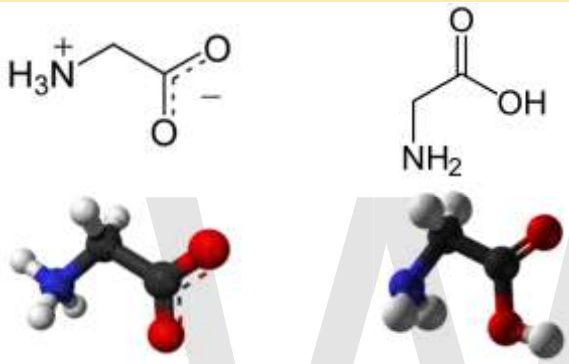
Cellular arginine biosynthetic capacity determined by activity of argininosuccinate synthetase (AS) is induced by the same mediators of septic response—endotoxin and cytokines—that induce nitric oxide synthase (NOS), the enzyme responsible for nitric oxide synthesis.

Malate salt

The malate salt of arginine can also be used during the treatment of alcoholic hepatitis and advanced cirrhosis.

Chapter- 12

Glycine

Glycine	
	
IUPAC name Glycine **Other names** Aminoethanoic acid Aminoacetic acid	
Identifiers	
Abbreviations	**Gly**, **G**
CAS number	56-40-6 ✓
PubChem	750
ChemSpider	730 ✓
UNII	TE7660XO1C ✓
EC-number	200-272-2
KEGG	D00011 ✓
ChEMBL	CHEMBL773 ✓
IUPHAR ligand	727
Properties	
Molecular formula	$C_2H_5NO_2$
Molar mass	75.07 g mol^{-1}
Appearance	white solid
Density	1.1607 g/cm^3
Melting point	233 °C (decomposition)
Solubility in water	25 g/100 mL
Solubility	soluble in ethanol, pyridine insoluble in ether
Acidity (pK_a)	2.34 (carboxyl), 9.6 (amino)

Hazards	
MSDS	External MSDS
LD_{50}	2600 mg/kg (mouse, oral)
Supplementary data page	
Structure and properties	*n*, ε_r, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

Glycine (abbreviated as **Gly** or **G**) is an organic compound with the formula NH_2CH_2COOH. With only two hydrogen atoms as its 'side chain', glycine is the smallest of the 20 amino acids commonly found in proteins. Its codons are GGU, GGC, GGA, GGG.

Glycine is a colourless, sweet-tasting crystalline solid. It is unique among the proteinogenic amino acids in that it is not chiral. It can fit into hydrophilic or hydrophobic environments, due to its two hydrogen atom side chain.

Production and key properties

Glycine was discovered in 1820, by Henri Braconnot who boiled gelatin with sulfuric acid.

Glycine is manufactured industrially by treating chloroacetic acid with ammonia:

$$ClCH_2COOH + 2\ NH_3 \rightarrow H_2NCH_2COOH + NH_4Cl$$

About 15 million kg are produced annually in this way.

In the USA (by GEO Specialty Chemicals, Inc.) and in Japan (by Shoadenko), glycine is produced via the Strecker amino acid synthesis.

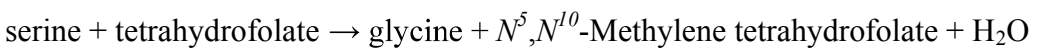
There are two producers of glycine in the United States. Chattem Chemicals, Inc., purchased by Sun Pharmaceutical, who is an international pharmaceutical company based in Mumbai, India and GEO Specialty Chemicals, Inc., who purchased the glycine and naphthalene sulfonate production facilities of Dow/Hampshire Chemical Corp.

Chattem's manufacturing process ("MCA" process) occurs in batches and results in a finished product with some residual chloride but no sulfate, while GEO's manufacturing process is considered a semi-batch process and results in a finished product with some residual sulfate but no chloride.

Its pK values are 2.35 and 9.78, so above pH 9.78, most of the glycine exists as the anionic amine, $H_2NCH_2CO_2^-$. Below pH 2.35, its solutions contain mostly the cationic carboxylic acid $H_3N^+CH_2CO_2H$. Its isoelectric point (pI) is 6.06.

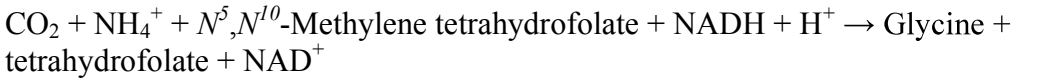
Biosynthesis

Glycine is not essential to the human diet, as it is biosynthesized in the body from the amino acid serine, which is in turn derived from 3-phosphoglycerate. In most organisms, the enzyme Serine hydroxymethyltransferase catalyses this transformation via the cofactor pyridoxal phosphate:



serine + tetrahydrofolate → glycine + N^5,N^{10}-Methylene tetrahydrofolate + H_2O

In the liver of vertebrates, glycine synthesis is catalyzed by glycine synthase (also called glycine cleavage enzyme). This conversion is readily reversible:

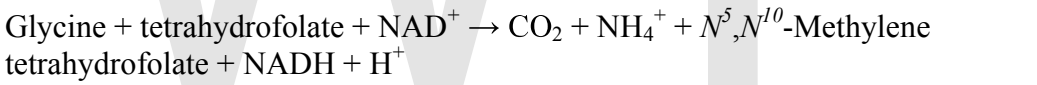


$CO_2 + NH_4^+ + N^5,N^{10}$-Methylene tetrahydrofolate + NADH + H^+ → Glycine + tetrahydrofolate + NAD^+

Glycine is coded by codons GGU, GGC, GGA and GGG. Most proteins incorporate only small quantities of glycine. A notable exception is collagen, which contains about 35% glycine.

Degradation

Glycine is degraded via three pathways. The predominant pathway in animals involves the catalysis of glycine cleavage enzyme, the same enzyme also involved in the biosynthesis of glycine. The degradation pathway is the reverse of this synthetic pathway:



Glycine + tetrahydrofolate + NAD^+ → $CO_2 + NH_4^+ + N^5,N^{10}$-Methylene tetrahydrofolate + NADH + H^+

In the second pathway, glycine is degraded in two steps. The first step is the reverse of glycine biosynthesis from serine with serine hydroxymethyl transferase. Serine is then converted to pyruvate by serine dehydratase.

In the third pathway of glycine degradation, glycine is converted to glyoxylate by D-amino acid oxidase. Glyoxylate is then oxidized by hepatic lactate dehydrogenase to oxalate in an NAD^+-dependent reaction.

The half-life of glycine and its elimination from the body varies significantly based on dose. In one study, the half-lfe was between 0.5 and 4.0 hours.

Physiological function

The principal function of glycine is as a precursor to proteins. It is also a building block to numerous natural products.

As a biosynthetic intermediate

In higher eukaryotes, D-Aminolevulinic acid, the key precursor to porphyrins, is biosynthesized from glycine and succinyl-CoA. Glycine provides the central C_2N subunit of all purines.

As a neurotransmitter

Glycine is an inhibitory neurotransmitter in the central nervous system, especially in the spinal cord, brainstem, and retina. When glycine receptors are activated, chloride enters the neuron via ionotropic receptors, causing an Inhibitory postsynaptic potential (IPSP). Strychnine is a strong antagonist at ionotropic glycine receptors, whereas bicuculline is a weak one. Glycine is a required co-agonist along with glutamate for NMDA receptors. In contrast to the inhibitory role of glycine in the spinal cord, this behaviour is facilitated at the (NMDA) glutaminergic receptors which are excitatory. The LD_{50} of glycine is 7930 mg/kg in rats (oral), and it usually causes death by hyperexcitability.

There is some evidence showing that 3000 milligrams of glycine before bedtime improves sleep quality.

Commercial uses

In the US, glycine is typically sold in two grades: United States Pharmacopeia ("USP"), and technical grade. Most glycine is manufactured as USP grade material for diverse uses. USP grade sales account for approximately 80 to 85 percent of the U.S. market for glycine.

- Pharmaceutical grade glycine is produced for some pharmaceutical applications, such as intravenous injections, where the customer's purity requirements often exceed the minimum required under the USP grade designation. Pharmaceutical grade glycine is often produced to proprietary specifications and is typically sold at a premium over USP grade glycine.
- Technical grade glycine, which may or may not meet USP grade standards, is sold for use in industrial applications; e.g., as an agent in metal complexing and finishing. Technical grade glycine is typically sold at a discount to USP grade glycine.

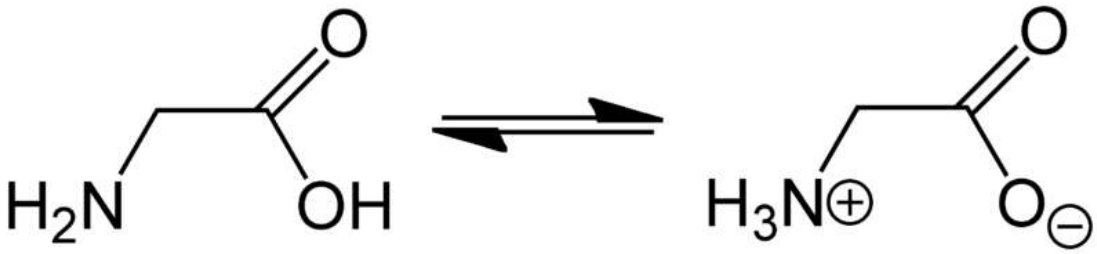
Animal and human foods

Other markets for USP grade glycine include its use an additive in pet food and animal feed. For humans, glycine is sold as a sweetener/taste enhancer. Food supplements and protein drinks contain glycine. Certain drug formulations include glycine to improve gastric absorption of the drug.

Cosmetics and miscellaneous applications

Glycine serves as a buffering agent in antacids, analgesics, antiperspirants, cosmetics, and toiletries.

Many miscellaneous products use glycine or its derivatives, such as the production of rubber sponge products, fertilizers, metal complexants.



Zwitterionic salts of glycine at neutral pH

Chemical feedstock

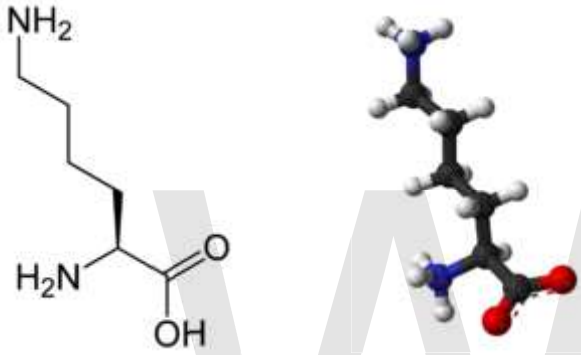
Glycine is an intermediate in the synthesis of a variety of chemical products. It is used in the manufacture of the herbicide glyphosate. Glyphosate is a non-selective systemic herbicide used to kill weeds, especially perennials and broadcast or used in the cut-stump treatment as a forestry herbicide. Initially, glyphosate was sold only by Monsanto under the tradename Roundup, but is no longer under patent.

Presence in space

The detection of glycine in the interstellar medium has been debated. In 2008, the glycine-like molecule aminoacetonitrile was discovered in the Large Molecule Heimat, a giant gas cloud near the galactic center in the constellation Sagittarius by the Max Planck Institute for Radio Astronomy. In 2009, glycine sampled in 2004 from comet Wild 2 by the NASA spacecraft Stardust was confirmed, the first discovery of extraterrestrial glycine. That mission's results bolstered the theory of panspermia, which claims that the "seeds" of life are widespread throughout the universe.

Chapter- 13

Lysine

Lysine	
	
IUPAC name Lysine **Other names** 2,6-diaminohexanoic acid	
Identifiers	
CAS number	70-54-2, 56-87-1 L, 923-27-3 D
PubChem	866
ChemSpider	843 ✓, 5747 L
KEGG	C16440 ✓
ChEMBL	CHEMBL28328 ✓
IUPHAR ligand	724
Properties	
Molecular formula	$C_6H_{14}N_2O_2$
Molar mass	146.19 g mol^{-1}
Supplementary data page	
Structure and properties	*n*, ε_r, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

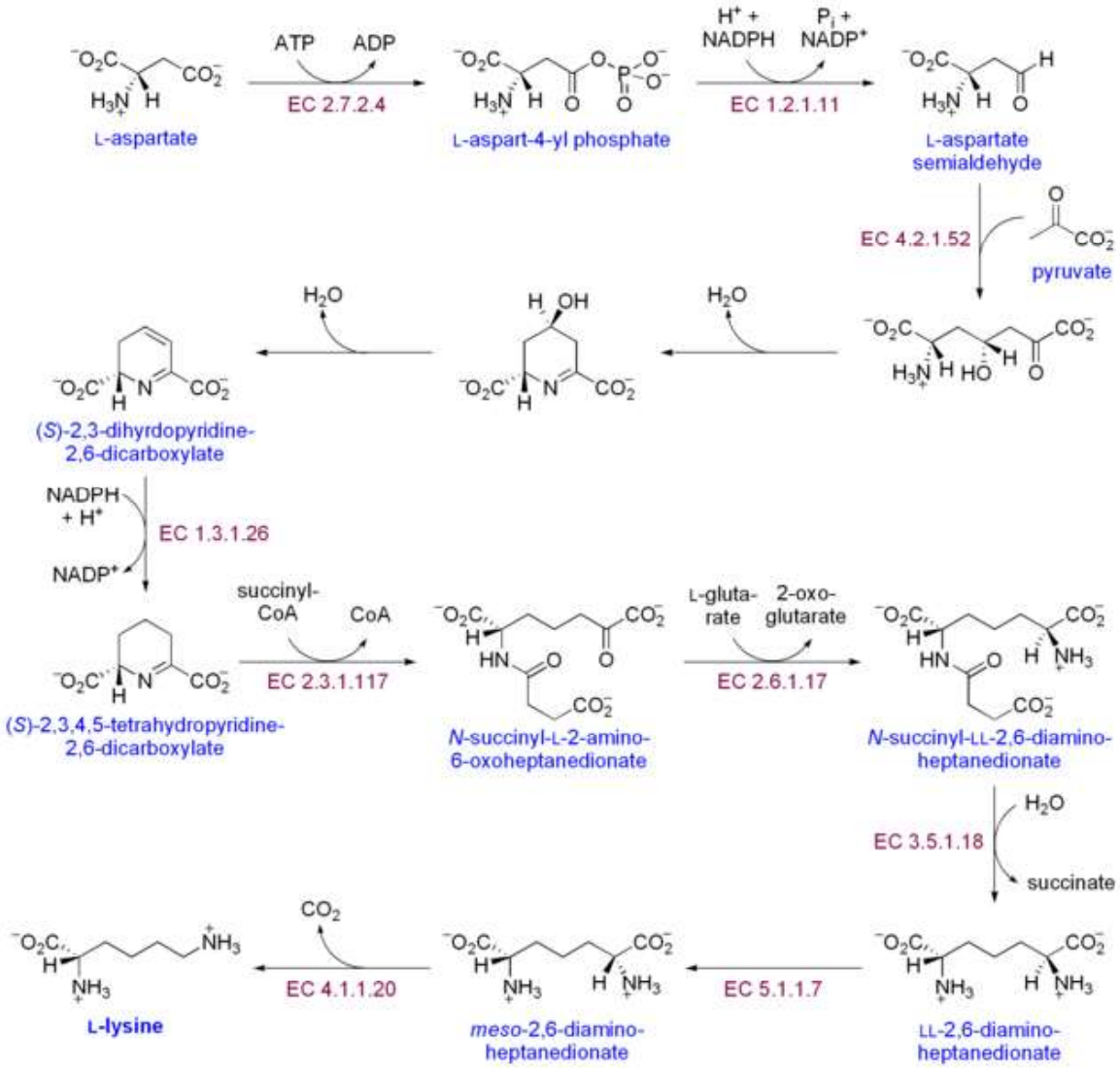
Lysine (abbreviated as **Lys** or **K**) is an α-amino acid with the chemical formula $HO_2CCH(NH_2)(CH_2)_4NH_2$. It is an essential amino acid, which means that the human body cannot synthesize it. Its codons are AAA and AAG.

Lysine is a base, as are arginine and histidine. The ε-amino group often participates in hydrogen bonding and as a general base in catalysis. Common posttranslational modifications include methylation of the ε-amino group, giving methyl-, dimethyl-, and trimethyllysine. The latter occurs in calmodulin. Other posttranslational modifications at lysine residues include acetylation and ubiquitination. Collagen contains hydroxylysine which is derived from lysine by lysyl hydroxylase. *O*-Glycosylation of lysine residues in the endoplasmic reticulum or Golgi apparatus is used to mark certain proteins for secretion from the cell.

Biosynthesis

As an essential amino acid, lysine is not synthesized in animals, hence it must be ingested as lysine or lysine-containing proteins. In plants and bacteria, it is synthesized from aspartic acid (aspartate):

- L-aspartate is first converted to L-aspartyl-4-phosphate by aspartokinase (or Aspartate kinase). ATP is needed as an energy source for this step.
- β-aspartate semialdehyde dehydrogenase converts this into β-aspartyl-4-semialdehyde (or β-aspartate-4-semialdehyde). Energy from NADPH is used in this conversion.
- Dihydrodipicolinate synthase adds a pyruvate group to the β-aspartyl-4-semialdehyde, and two water molecules are removed. This causes cyclization and gives rise to 2,3-dihydrodipicolinate.
- This product is reduced to 2,3,4,5-tetrahydrodipicolinate (or Δ^1-piperidine-2,6-dicarboxylate, in the figure: (S)-2,3,4,5-tetrahydropyridine-2,6-dicarboxylate) by dihydrodipicolinate reductase. This reaction consumes a NADPH molecule.
- Tetrahydrodipicolinate N-acetyltransferase opens this ring and gives rise to N-succinyl-L-2-amino-6-oxoheptanedionate (or N-acyl-2-amino-6-oxopimelate). Two water molecules and one acyl-CoA (succinyl-CoA) enzyme are used in this reaction.
- N-succinyl-L-2-amino-6-oxoheptanedionate is converted into N-succinyl-LL-2,6-diaminoheptanedionate (N-acyl-2,6-diaminopimelate). This reaction is catalyzed by the enzyme succinyl diaminopimelate aminotransferase. A glutaric acid molecule is used in this reaction and an oxoacid is produced as a byproduct.
- N-succinyl-LL-2,6-diaminoheptanedionate (N-acyl-2,6-diaminopimelate)is converted into LL-2,6-diaminoheptanedionate (L,L-2,6-diaminopimelate) by succinyl diaminopimelate desuccinylase (acyldiaminopimelate deacylase). A water molecule is consumed in this reaction and a succinate is produced a byproduct.
- LL-2,6-diaminoheptanedionate is converted by diaminopimelate epimerase into meso-2,6-diamino-heptanedionate (meso-2,6-diaminopimelate).
- Finally meso-2,6-diamino-heptanedionate is converted into L-lysine by diaminopimelate decarboxylase.



Enzymes involved in this biosynthesis include:

1. Aspartokinase
2. β-aspartate semialdehyde dehydrogenase
3. Dihydropicolinate synthase
4. Δ^1-piperidine-2,6-dicarboxylate dehydrogenase
5. *N*-succinyl-2-amino-6ketopimelate synthase
6. Succinyl diaminopimelate aminotransferase
7. Succinyl diaminopimelate desuccinylase
8. Diaminopimelate epimerase
9. Diaminopimelate decarboxylase.

Metabolism

Lysine is metabolised in mammals to give acetyl-CoA, via an initial transamination with α-ketoglutarate. The bacterial degradation of lysine yields cadaverine by decarboxylation.

Allysine is a derivative of lysine, used in the production of elastin and collagen. It is produced by the actions of the enzyme lysyl oxidase on lysine in the extracellular matrix and is essential in the crosslink formation that stabilizes collagen and elastin.

Synthesis

Synthetic, racemic lysine has long been known. A practical synthesis starts from caprolactam. Industrially, L-lysine is usually manufactured by a fermentation process using Corynebacterium glutamicum; production exceeds 600,000 tons a year.

Dietary sources

The nutritional requirement per day, in milligrams of lysine per kilogram of body weight, is: infants (3–4 months) 103, children (2 years) 64, older children (10–12 years) 60 to 44, adults 12. For a 70 kg adult, 12 milligrams of lysine per kilogram of body weight is 0.84 grams of lysine.

Lysine is the limiting amino acid (the essential amino acid found in the smallest quantity in the particular foodstuff) in most cereal grains, but is plentiful in most pulses (legumes). Consequently, meals that combine cereal grains and legumes, such as the Indian dal with rice, Middle Eastern hummus, ful medames, falafel with pita bread, the Mexican beans with rice or tortilla have arisen to provide complete protein in diets that are, by choice or by necessity, vegetarian. A food is considered to have sufficient lysine if it has at least 51 mg of lysine per gram of protein (so that the protein is 5.1% lysine).

Foods containing significant amounts of lysine include:

- Catfish, channel, farmed, raw: 9.19% of the protein is lysine.
- Chicken, roasting, meat and skin, cooked, roasted: 8.11% of the protein is lysine.
- Beef, ground, 90% lean/10% fat, cooked: 8.31% of the protein is lysine.
- Soybean, mature seeds, raw: 7.42% of the protein is lysine.
- Soybean, mature seeds, sprouts: 5.74% of the protein is lysine (sprouting decreases the lysine content).
- Winged Bean (aka Goa Bean or Asparagus Pea), mature seeds, raw: 7.20% of the protein is lysine.
- Lentil, pink, raw: 6.97% of the protein is lysine.
- Lentil, sprouts, raw: 7.95% of the protein is lysine (sprouting increases the lysine content).
- Parmesan cheese, grated: 7.75% of the protein is lysine.
- Azuki bean (adzuki beans), mature seeds, raw: 7.53% of the protein is lysine.
- Milk, non-fat: 7.48% of the protein is lysine.

- Egg (food), whole, raw: 7.27% of the protein is lysine.
- Pea, split, mature seeds, raw: 7.22% of the protein is lysine.
- Kidney Bean, mature seeds, raw: 6.87% of the protein is lysine.
- Chickpea, (garbanzo beans, bengal gram), mature seeds, raw: 6.69% of the protein is lysine.
- Navy Bean, mature seeds, raw: 5.73% of the protein is lysine.
- Amaranth, grain, uncooked: 5.17% of the protein is lysine.

Good sources of lysine are foods rich in protein such as soy, as well as meat (specifically red meat, lamb, pork, and poultry), cheese (particularly Parmesan), certain fish (such as cod and sardines), and eggs.

Properties

L-Lysine is a necessary building block for all protein in the body. L-Lysine plays a major role in calcium absorption; building muscle protein; recovering from surgery or sports injuries; and the body's production of hormones, enzymes, and antibodies.

Modifications

Lysine can be modified through acetylation, methylation, ubiquitination, sumoylation, neddylation, biotinylation and carboxylation which tends to modify the function of the protein of which the modified lysine residue(s) are a part.

Clinical significance

It has been suggested that lysine may be beneficial for those with herpes simplex infections. However, more research is needed to fully substantiate this claim. For more information, refer to Herpes simplex - Lysine.

Lysine has a known anxiolytic action through its effects on serotonin receptors in the intestinal tract. One study on rats showed that overstimulation of the 5-HT4 receptors in the gut are associated with anxiety-induced intestinal pathology. Lysine, acting as a serotonin antagonist and therefore reducing the overactivity of these receptors, reduced signs of anxiety and anxiety-induced diarrhea in the sample population. Another study showed that lysine deficiency leads to a pathological increase in serotonin in the amygdala, a brain structure that is involved in emotional regulation and the stress response.

Human studies have also shown negative correlations between lysine intake and anxiety. A population-based study in Syria included 93 families whose diet is primarily grain-based and therefore likely to be deficient in lysine. Fortification of grains with lysine was shown to reduce markers of anxiety, including cortisol levels, and also led to potentiation of benzodiazepine receptors (common targets of anxiolytic drugs such as Xanax and Ativan).

There are Lysine conjugates that show promise in the treatment of cancer, by causing cancerous cells to destroy themselves when the drug is combined with the use of phototherapy, while leaving non-cancerous cells unharmed.

While chemically insignificant to lysine itself, it is worth noting that lysine is attached to dextroamphetamine to form the prodrug lisdexamfetamine (Vyvanse). In the gastrointestinal tract, the lysine molecule is cleaved from the dextroamphetamine, thereby making oral administration necessary.

According to animal studies, lysine deficiency causes immunodeficiency. One cause of relative lysine deficiency is cystinuria, where there is impaired hepatic resorption of basic, or positively charged amino acids, including lysine. The accompanying urinary cysteine results because the same deficient amino acid transporter is normally present in the kidney as well.

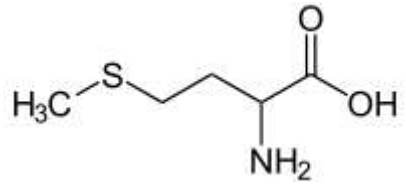
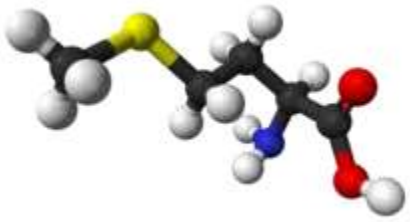
Use of lysine in animal feed

Lysine production for animal feed is a major global industry, reaching in 2009 almost 700,000 tonnes for a market value of over €1.22 billion. Lysine is an important additive to animal feed because it is a limiting amino acid when optimizing the growth of certain animals such as pigs and chickens for the production of meat. Lysine supplementation allows for the use of lower-cost plant protein (maize, for instance, rather than soy) while maintaining high growth rates, and limiting the pollution from nitrogen excretion.

Lysine is industrially produced by microbial fermentation, from a base mainly of sugar. Research through genetic engineering of bacterial strains to improve the efficiency of the production and allow it to me made from other substrates is actively pursued.

Chapter- 14

Methionine

Methionine	
  IUPAC name Methionine **Other names** 2-amino-4-(methylthio)butanoic acid	
Identifiers	
Abbreviations	Met, M
CAS number	59-51-8 ✓, 63-68-3 (L-isomer) ✓, 348-67-4 (D-isomer) ✓
PubChem	876
ChemSpider	853 ✓, 5907 (L-isomer)
UNII	73JWT2K6T3 ✓
EC-number	200-432-1
KEGG	D04983 ✗
ChEMBL	CHEMBL42336 ✗
ATC code	V03AB26,QA05BA90, QG04BA90
Properties	
Molecular formula	$C_5H_{11}NO_2S$
Molar mass	149.21 g mol^{-1}
Appearance	White crystalline powder
Density	1.340 g/cm^3
Melting point	281 °C decomp.
Solubility in	Soluble

water	
Acidity (pK_a)	2.28 (carboxyl), 9.21 (amino)
Supplementary data page	
Structure and properties	*n*, ε_r, etc.
Thermodynamic data	Phase behaviour Solid, liquid, gas
Spectral data	UV, IR, NMR, MS

Methionine is an α-amino acid with the chemical formula $HO_2CCH(NH_2)CH_2CH_2SCH_3$. This essential amino acid is classified as nonpolar.

Function

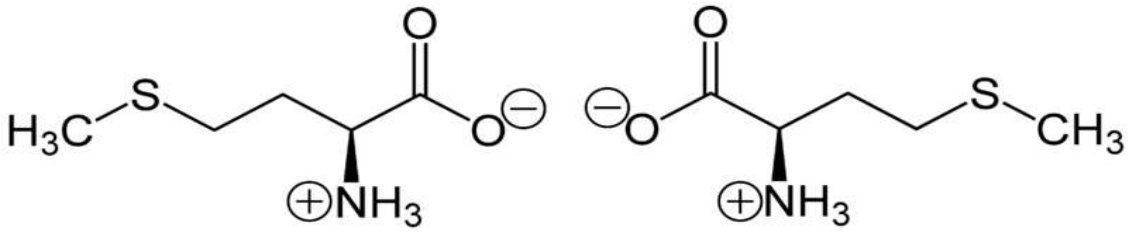
Together with cysteine, methionine is one of two sulfur-containing proteinogenic amino acids. Its derivative *S*-adenosyl methionine (SAM) serves as a methyl donor. Methionine is an intermediate in the biosynthesis of cysteine, carnitine, taurine, lecithin, phosphatidylcholine, and other phospholipids. Improper conversion of methionine can lead to atherosclerosis.

This amino acid is also used by plants for synthesis of ethylene. The process is known as the Yang Cycle or the methionine cycle.

Methionine is one of only two amino acids encoded by a single codon (AUG) in the standard genetic code (tryptophan, encoded by UGG, is the other). The codon AUG is also the "Start" message for a ribosome that signals the initiation of protein translation from mRNA. As a consequence, methionine is incorporated into the N-terminal position of all proteins in eukaryotes and archaea during translation, although it is usually removed by post-translational modification. In bacteria, the derivative N-formylmethionine is used as the initial amino acid.

Rats fed a diet without methionine developed steatohepatitis. Administration of methionine ameliorated the pathological consequences of methionine deprivation.

Betaines



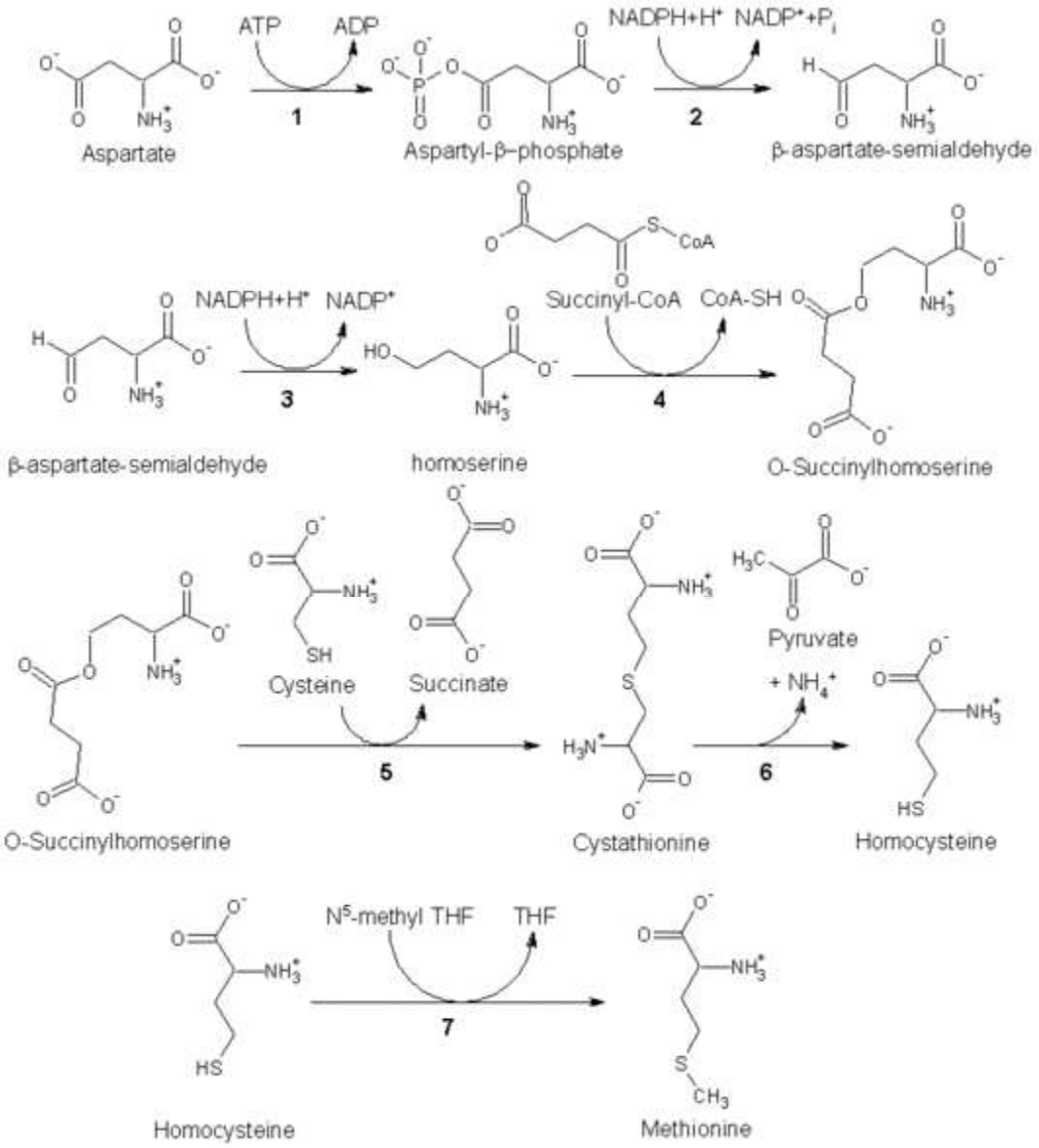
(*S*)-Methionine (left) and (*R*)-methionine (right) in zwitterionic form at neutral pH

Biosynthesis

As an essential amino acid, methionine is not synthesized de novo in humans, hence we must ingest methionine or methionine-containing proteins. In plants and microorganisms, methionine is synthesized via a pathway that uses both aspartic acid and cysteine. First, aspartic acid is converted via β-aspartyl-semialdehyde into homoserine, introducing the pair of contiguous methylene groups. Homoserine converts to *O*-succinyl homoserine, which then reacts with cysteine to produce cystathionine, which is cleaved to yield homocysteine. Subsequent methylation of the thiol group by folates affords methionine. Both cystathionine-γ-synthase and cystathionine-β-lyase require pyridoxyl-5'-phosphate as a cofactor, whereas homocysteine methyltransferase requires vitamin B_{12} as a cofactor.

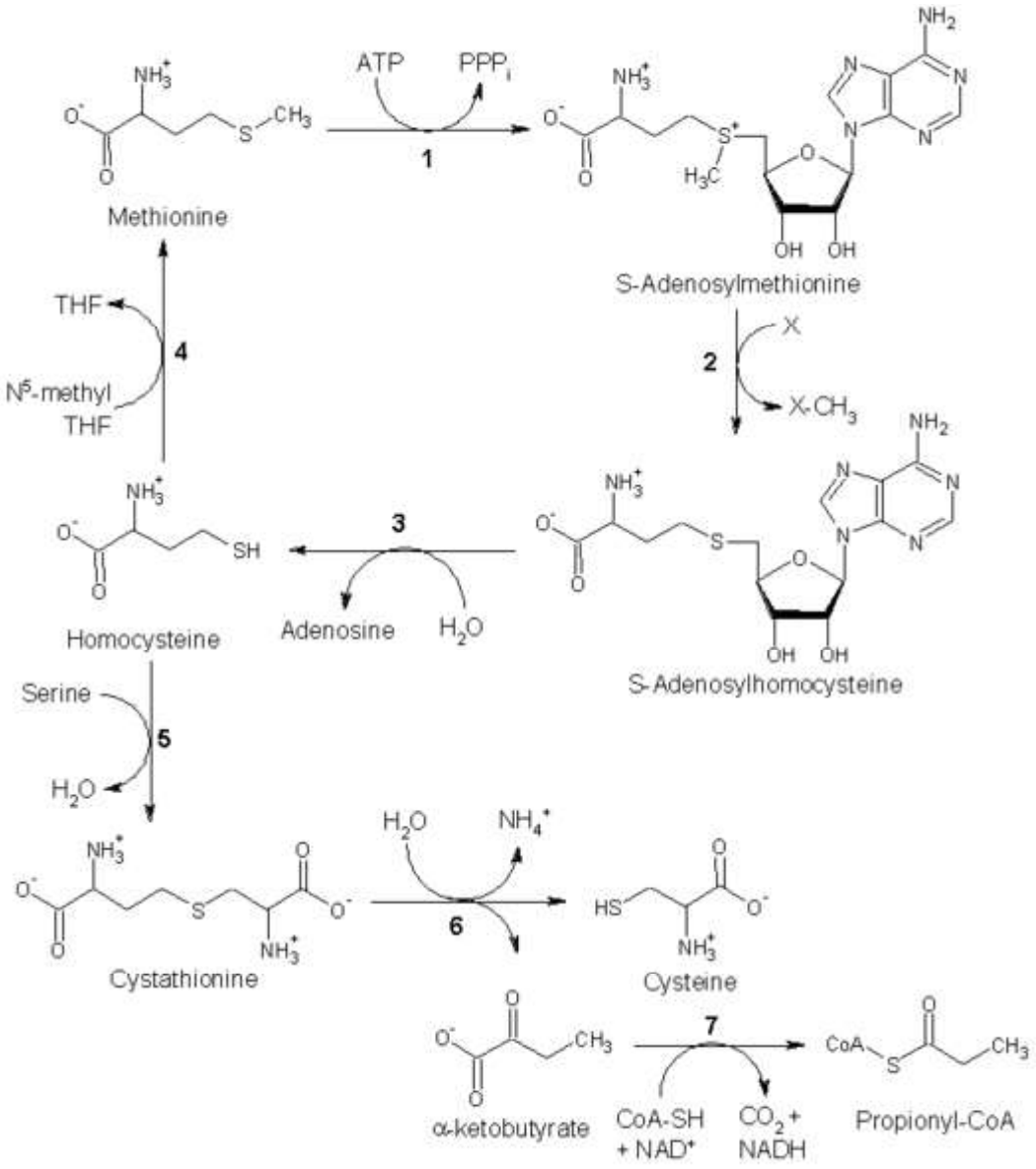
Enzymes involved in methionine biosynthesis:

1. aspartokinase
2. β-aspartate semialdehyde dehydrogenase
3. homoserine dehydrogenase
4. homoserine O-transsuccinylase
5. cystathionine-γ-synthase
6. cystathionine-β-lyase
7. methionine synthase (in mammals, this step is performed by homocysteine methyltransferase)



Methionine biosynthesis

Other biochemical pathways



Fates of methionine

Although mammals cannot synthesize methionine, they can still use it in a variety of biochemical pathways:

Generation of homocysteine

Methionine is converted to S-adenosylmethionine (SAM) by (1) methionine adenosyltransferase.

SAM serves as a methyl-donor in many (2) methyltransferase reactions, and is converted to *S*-adenosylhomocysteine (SAH).

(3) Adenosylhomocysteinase converts SAH to homocysteine.

There are two fates of homocysteine: it can be used to regenerate methionine, or to form cysteine.

Regeneration of methionine

Methionine can be regenerated from homocysteine via (4) methionine synthase.

Homocysteine can also be remethylated using glycine betaine (NNN-trimethyl glycine, TMG) to methionine via the enzyme betaine-homocysteine methyltransferase (E.C.2.1.1.5, BHMT). BHMT makes up to 1.5% of all the soluble protein of the liver, and recent evidence suggests that it may have a greater influence on methionine and homocysteine homeostasis than methionine synthase.

Conversion to cysteine

Homocysteine can be converted to cysteine.

- (5) Cystathionine-β-synthase (a PLP-dependent enzyme) combines homocysteine and serine to produce cystathionine. Instead of degrading cystathionine via cystathionine-β-lyase, as in the biosynthetic pathway, cystathionine is broken down to cysteine and α-ketobutyrate via (6) cystathionine-γ-lyase.
- (7) The enzyme α-ketoacid dehydrogenase converts α-ketobutyrate to propionyl-CoA, which is metabolized to succinyl-CoA in a three-step process.

Synthesis

Racemic methionine can be synthesized from diethyl sodium phthalimidomalonate by alkylation with chloroethylmethylsulfide ($ClCH_2CH_2SCH_3$) followed by hydrolysis and decarboxylation.

Dietary sources

Food sources of Methionine

Food	g/100g
Sesame seeds flour (low fat)	1.656
Brazil nuts	1.008
Soy protein concentrate	0.814
Wheat germ	0.456
Oat	0.312
Peanuts	0.309

Chickpea	0.253
Corn, yellow	0.197
Almonds	0.151
Beans, pinto, cooked	0.117
Lentils, cooked	0.077
Rice, brown, medium-grain, cooked	0.052

High levels of methionine can be found in sesame seeds, Brazil nuts, fish, meats and some other plant seeds; methionine is also found in cereal grains. Most fruits and vegetables contain very little of it. Most legumes are also low in methionine. The complement of cereal (methionine) and legumes (lysine), providing a complete protein, is a classic combination, found throughout the world, such as in rice and beans or tortilla and beans.

Racemic methionine is sometimes added as an ingredient to pet foods.

Methionine restriction

There is a growing body of evidence that shows restricting methionine consumption can increase lifespans in some animals.

A 2005 study showed methionine restriction without energy restriction extends mouse lifespan.

A study published in *Nature* showed adding just the essential amino acid methionine to fruit flies on a calorie restricted diet restored egg-laying without reducing lifespan.

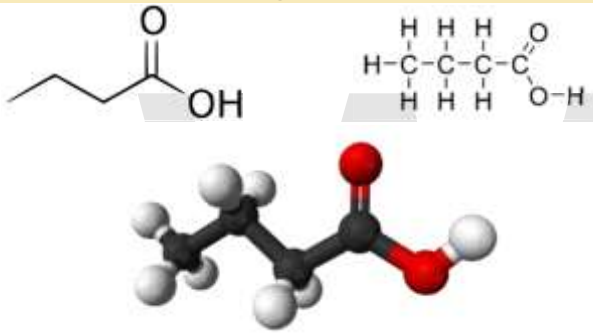
Other Uses

DL-methionine is sometimes given as a supplement to dogs; it helps keep dogs from damaging grass by reducing the pH of the urine. One example is "Grass Saver" by NaturVet.

Chapter- 15

Butyric Acid and Caprylic Acid

Butyric acid

Butyric acid	
	
IUPAC name Butanoic acid	
Other names Butyric acid; 1-Propanecarboxylic acid; Propanecarboxylic acid; C4:0 (Lipid numbers)	
Identifiers	
CAS number	107-92-6 ✓
PubChem	264
ChemSpider	259 ✓
UNII	40UIR9Q29H ✓
UN number	2820
KEGG	C00246 ✓
MeSH	Butyric+acid
ChEMBL	CHEMBL14227 ✓
IUPHAR ligand	1059
Properties	
Molecular formula	$C_4H_8O_2$
Molar mass	88.11 g mol^{-1}
Appearance	Colorless liquid
Density	0.9595 g/mL
Melting point	−7.9 °C, 265 K, 18 °F
Boiling point	163.5 °C, 437 K, 326 °F
Solubility in water	miscible

Acidity (pK_a)	4.82
Refractive index (n_D)	1.3980 (19 °C)
Viscosity	0.1529 cP
Hazards	
MSDS	External MSDS
R-phrases	R20 R21 R22 R34 R36 R37 R38
Flash point	72 °C
Autoignition temperature	452 °C
Related compounds	
Other anions	butyrate
Related carboxylic acids	propionic acid acrylic acid succinic acid malic acid tartaric acid crotonic acid fumaric acid pentanoic acid
Related compounds	butanol butyraldehyde methyl butyrate

Butyric acid (from Greek βούτυρος = *butter*), also known under the systematic name **butanoic acid**, is a carboxylic acid with the structural formula $CH_3CH_2CH_2$-COOH. Salts and esters of butyric acid are known as **butyrates** or **butanoates**. Butyric acid is found in butter, parmesan cheese, vomit, and as a product of anaerobic fermentation (including in the colon and as body odor). It has an unpleasant smell and acrid taste, with a sweetish aftertaste (similar to ether). It can be detected by mammals with good scent detection abilities (such as dogs) at 10 ppb, whereas humans can detect it in concentrations above 10 ppm.

Chemistry

Butyric acid is a fatty acid occurring in the form of esters in animal fats and plant oils. The triglyceride of butyric acid makes up 3% to 4% of butter. When butter goes rancid, butyric acid is liberated from the glyceride by hydrolysis leading to the unpleasant odor. It is an important member of the fatty acid sub-group called short-chain fatty acids. Butyric acid is a weak acid with a pKa of 4.82, similar to acetic acid which has pKa 4.76. The similar strength of these acids results from their common -CH_2COOH terminal structure. Pure butyric acid is 10.9 molar.

The acid is an oily colorless liquid that is easily soluble in water, ethanol, and ether, and can be separated from an aqueous phase by saturation with salts such as calcium chloride. Potassium dichromate and sulfuric acid oxidize it to carbon dioxide and acetic acid, while alkaline potassium permanganate oxidizes it to carbon dioxide. The calcium salt, $Ca(C_4H_7O_2)_2 \cdot H_2O$, is less soluble in hot water than in cold.

Butyric acid has a structural isomer called isobutyric acid (2-methylpropanoic acid).

Production

It is industrially prepared by the fermentation of sugar or starch, brought about by the addition of putrefying cheese, with calcium carbonate added to neutralize the acids formed in the process. The butyric fermentation of starch is aided by the direct addition of *Bacillus subtilis*. Salts and esters of the acid are called butanoates.

Butyric acid or fermentation butyric acid is also found as a hexyl ester (hexyl butanoate) in the oil of *Heracleum giganteum* (a type of hogweed) and as an octyl ester (octyl butanoate) in parsnip (*Pastinaca sativa*); it has also been noticed in the fluors of the flesh and in perspiration.

Uses

Butyric acid is used in the preparation of various butanoate esters. Low-molecular-weight esters of butyric acid, such as methyl butanoate, have mostly pleasant aromas or tastes. As a consequence, they find use as food and perfume additives.

Due to its powerful odor, it has also been used as a fishing bait additive. Many of the commercially available flavours used in carp (*Cyprinus carpio*) baits use butyric acid as their ester base; however, it is not clear whether fish are attracted by the butyric acid itself or the additional substances added to it. Butyric acid was, however, one of the few organic acids shown to be palatable for both tench and bitterling.

The substance has also been used as a noxious, nausea-inducing repellent by anti-whaling protesters, against Japanese whaling crews, as well as by anti-abortion protestors to disrupt and harass clinics.

Biological functionality

Butanoate fermentation

Butanoate is produced as end-product of a fermentation process solely performed by obligate anaerobic bacteria. Fermented Kombucha "tea" includes butyric acid as a result of the fermentation. This fermentation pathway was discovered by Louis Pasteur in 1861. Examples of butanoate-producing species of bacteria:

- *Clostridium acetobutylicum*
- *Clostridium butyricum*
- *Clostridium kluyveri*
- *Clostridium pasteurianum*
- *Fusobacterium nucleatum*
- *Butyrivibrio fibrisolvens*
- *Eubacterium limosum*

The pathway starts with the glycolytic cleavage of glucose to two molecules of pyruvate, as happens in most organisms. Pyruvate is then oxidized into acetyl coenzyme A using a unique mechanism that involves an enzyme system called pyruvate-ferredoxin oxidoreductase. Two molecules of carbon dioxide (CO_2) and two molecules of elemental hydrogen (H_2) are formed as wastes products from the cell. Then,

Action	Responsible enzyme
Acetyl coenzyme A converts into acetoacetyl coenzyme A	acetyl-CoA-acetyl transferase
Acetoacetyl coenzyme A converts into β-hydroxybutyryl CoA	β-hydroxybutyryl-CoA dehydrogenase
β-hydroxybutyryl CoA converts into crotonyl CoA	crotonase
Crotonyl CoA converts into butyryl CoA ($CH_3CH_2CH_2C{=}O\text{-}CoA$)	butyryl CoA dehydrogenase
A phosphate group replaces CoA to form butyryl phosphate	phosphobutyrylase
The phosphate group joins ADP to form ATP and butyrate	butyrate kinase

ATP is produced, as can be seen, in the last step of the fermentation. Three molecules of ATP are produced for each glucose molecule, a relatively high yield. The balanced equation for this fermentation is

$$C_6H_{12}O_6 \rightarrow C_4H_8O_2 + 2CO_2 + 2H_2.$$

Acetone and butanol fermentation

Several species form acetone and butanol in an alternative pathway, which starts as butyrate fermentation. Some of these species are

- *Clostridium acetobutylicum*, the most prominent acetone and butanol producer, used also in industry,
- *Clostridium beijerinckii*,
- *Clostridium tetanomorphum*,
- *Clostridium aurantibutyricum*.

These bacteria begin with butanoate fermentation as described above, but, when the pH drops below 5, they switch into butanol and acetone production in order to prevent further lowering of the pH. Two molecules of butanol are formed for each molecule of acetone.

The change in the pathway occurs after acetoacetyl CoA formation. This intermediate then takes two possible pathways:

- acetoacetyl CoA → acetoacetate → acetone, or

- acetoacetyl CoA → butyryl CoA → butanal → butanol.

Butyric acid function/activity

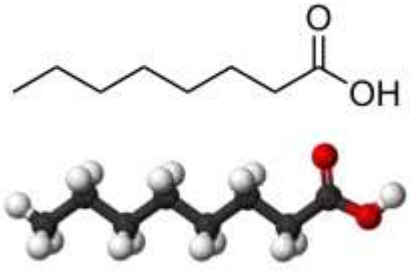
Highly-fermentable fiber residues, like resistant starch, oat bran, and pectin are transformed by colonic bacteria into short-chain fatty acids including butyrate. One study found that resistant starch consistently produces more butyrate than other types of dietary fiber.

The role of butyrate changes depending on its role in cancer or normal cells. This is known as the "butyrate paradox". Butyrate inhibits colonic tumor cells, and promotes healthy colonic epithelial cells; but the signaling mechanism is not well understood. A review suggested that the chemopreventive benefits of butanoate depend in part on amount, time of exposure with respect to the tumorigenic process, and the type of fat in the diet. Low carbohydrate, low fiber diets like the Atkins diet are known to reduce the amount of butyrate produced in the colon.

Butyric acid can act as an HDAC inhibitor, inhibiting the function of histone deacetylase enzymes, thereby favoring an acetylated state of histones in the cell. Acetylated histones have a lower affinity for DNA than non-acetylated histones, due to the neutralization of electrostatic charge interactions. In general, it is thought that transcription factors will be unable to access regions where histones are tightly associated with DNA (i.e. non-acetylated, e.g., heterochromatin). Therefore, it is thought that butyric acid enhances the transcriptional activity at promoters, which are typically silenced or downregulated due to histone deacetylase activity.

Two HDAC inhibitors, sodium butyrate (NaB) and trichostatin A (TSA), increase lifespan in experimental animals.

Caprylic acid

Caprylic acid

IUPAC name octanoic acid
Other names

C8:0 (Lipid numbers)

Identifiers	
CAS number	124-07-2 ✓
PubChem	379
ChemSpider	370 ✓
UNII	OBL58JN025 ✓
KEGG	D05220 ✓
ChEMBL	CHEMBL324846 ✓
Properties	
Molecular formula	$C_8H_{16}O_2$
Molar mass	144.21 g/mol
Appearance	Oily colorless liquid
Density	0.910 g/cm^3
Melting point	16.7 °C
Boiling point	237 °C, 510 K, 459 °F
Solubility in methanol	6.31 M
Acidity (pK_a)	4.89

Caprylic acid is the common name for the eight-carbon saturated fatty acid known by the systematic name **octanoic acid**. It is found naturally in the milk of various mammals, and it is a minor constituent of coconut oil and palm kernel oil. It is an oily liquid that is minimally soluble in water with a slightly unpleasant rancid-like smell.

Two other acids are named after goats: caproic (C6) and capric (C10). Along with caprylic acid these total 15% in goat milk fat.

Uses

Caprylic acid is used commercially in the production of esters used in perfumery and also in the manufacture of dyes.

Caprylic acid is also used in the treatment of some bacterial infections. Due to its relatively short chain length it has no difficulty in penetrating fatty cell wall membranes, hence its effectiveness in combating certain lipid-coated bacteria, such as *Staphylococcus aureus* and various species of *Streptococcus*.

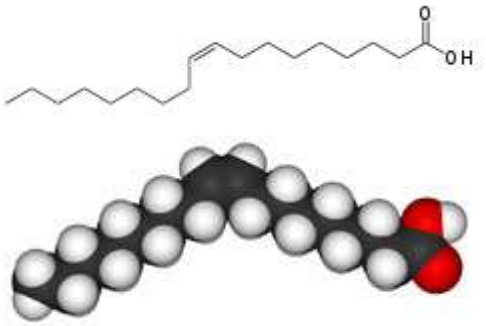
Caprylic acid is an antimicrobial pesticide used as a food contact surface sanitizer in commercial food handling establishments on dairy equipment, food processing equipment, breweries, wineries, and beverage processing plants. It is also used as disinfectant in health care facilities, schools/colleges, animal care/veterinary facilities, industrial facilities, office buildings, recreational facilities, retail and wholesale establishments, livestock premises, restaurants, and hotels/motels. In addition, caprylic acid is used as an algaecide, bactericide, and fungicide in nurseries, greenhouses, garden centers, and interiorscapes on ornamentals. Products containing caprylic acid are formulated as soluble concentrate/liquids and ready-to-use liquids.

Caprylic acid must be covalently linked to the serine residue at the 3-position of ghrelin, specifically, it must acylate the -OH group, for ghrelin to have its hunger-stimulating action on the feeding centers of the hypothalamus, though other fatty acids may have similar effects.

Chapter- 16

Oleic, Nervonic and Pentadecanoic Acid

Oleic acid

Oleic acid	
	
IUPAC name (9*Z*)-Octadec-9-enoic acid **Other names** (9*Z*)-Octadecenoic acid (*Z*)-Octadec-9-enoic acid *cis*-9-Octadecenoic acid *cis*-Δ^9-Octadecenoic acid Oleic acid 18:1 cis-9	
Identifiers	
CAS number	112-80-1 ✓
Properties	
Molecular formula	$C_{18}H_{34}O_2$
Molar mass	282.4614 g/mol
Appearance	Pale yellow or brownish yellow oily liquid with lard-like odor
Density	0.895 g/mL
Melting point	13-14 °C (286 K)
Boiling point	360 °C (633 K) (760mm Hg)
Solubility in water	Insoluble
Solubility in methanol	Soluble

Hazards	
MSDS	JT Baker

Oleic acid is a monounsaturated omega-9 fatty acid found in various animal and vegetable fats. It has the formula $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$. It is an odorless, colourless oil. The *trans* isomer of oleic acid is called elaidic acid (hence the name elaidinization for a reaction that switches *cis* isomers to *trans* isomers). The term "oleic" means related to, or derived from, oil or olive.

Occurrence

Triglyceride esters of oleic acid compose the majority of olive oil, although there may be less than 2.0% as actual free acid in the virgin olive oil, with higher concentrations making the olive oil inedible. It also makes up 59-75% of pecan oil, 36-67% of peanut oil, 15-20% of grape seed oil, sea buckthorn oil, and sesame oil, and 14% of poppyseed oil. It is also abundantly present in many animal fats, constituting 37 to 56% of chicken and turkey fat, and 44 to 47% of lard, etc.

Oleic acid is the most abundant fatty acid in human adipose tissue.

As an insect pheromone

Oleic acid is emitted by the decaying corpses of a number of insects, including bees and *Pogonomyrmex* ants, and triggers the instincts of living workers to remove the dead bodies from the hive. If a live bee or ant is daubed with oleic acid, it is dragged off as if it were dead. The oleic acid smell indicates to living insects how to avoid others that have succumbed to disease or places where predators lurk.

Production and chemical behavior

Oleic acid exhibits many of the reactions of carboxylic acids and alkenes. It is soluble in aqueous base to give salts called oleates. Iodine adds across the double bond. Hydrogenation of the double bond yields the saturated derivative called stearic acid. Oxidation at the double bond occurs slowly in air, and is known as rancidification in foodstuffs or drying in coatings. Reduction of the carboxylic acid group yields oleyl alcohol. Ozonolysis of oleic acid is an important route to azelaic acid. The coproduct is nonanoic acid:

$$H_{17}C_8CH=CHC_7H_{14}CO_2H + 4"O" \rightarrow H_{17}C_8CO_2H + HO_2CC_7H_{14}CO_2H$$

Esters of azelaic acid find applications in lubrication and plasticizers.

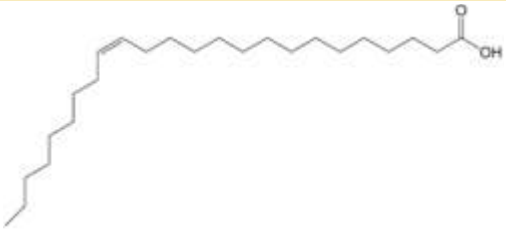
Uses

As an excipient in pharmaceuticals, oleic acid is used as an emulsifying or solubilizing agent in aerosol products.

Health effects

Oleic acid may hinder the progression of adrenoleukodystrophy (ALD), a fatal disease that affects the brain and adrenal glands. Oleic and monounsaturated fatty acid levels in the membranes of red blood cells have been associated with increased risk of breast cancer. Oleic acid may be responsible for the hypotensive (blood pressure reducing) effects of olive oil.

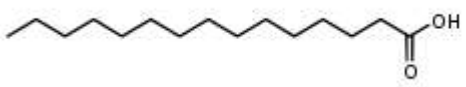
Nervonic acid

Nervonic acid	
	
IUPAC name (*Z*)-Tetracos-15-enoic acid **Other names** *cis*-15-Tetracosenoic acid 24:1 cis, delta 9 or 24:1 omega 9	
Identifiers	
CAS number	506-37-6
PubChem	5281120
ChemSpider	4444565 ✓
KEGG	C08323 ✓
ChEMBL	CHEMBL1173379 ✓
Properties	
Molecular formula	$C_{24}H_{46}O_2$
Molar mass	366.62 g/mol
Melting point	42-43 °C

Nervonic acid is a monounsaturated omega-9 fatty acid. Nervonic acid has been identified as important in the biosynthesis of nerve cell myelin. It is found in the sphingolipids of white matter in human brain.

Nervonic acid is used in the treatment of disorders involving demyelination, such as adrenoleukodystrophy and multiple sclerosis where there is a decreased level of nervonic acid in sphingolipids.

Pentadecanoic acid

Pentadecanoic acid

IUPAC name pentadecanoic acid
Other names *n*-Pentadecanoic acid; Pentadecylic acid
Identifiers
CAS number 1002-84-2
PubChem 13849
ChemSpider 13249
Properties
Molecular formula $C_{15}H_{30}O_2$
Molar mass 242.4 g mol^{-1}
Melting point 51-53 °C
Boiling point 257 °C (100 mmHg)

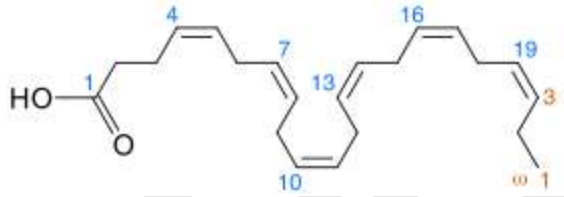
Pentadecanoic acid is a saturated fatty acid. Its molecular formula is $CH_3(CH_2)_{13}COOH$.

The butterfat in cows milk is its major dietary source and it is used as a marker for butterfat consumption.

Chapter- 17

Docosahexaenoic and Eicosapentaenoic Acid

Docosahexaenoic acid

Docosahexaenoic acid	
	
IUPAC name (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid; Doconexent	
Other names cervonic acid, DHA	
Identifiers	
CAS number	6217-54-5 ✓
PubChem	445580
ChemSpider	393183 ✓
UNII	ZAD9OKH9JC ✓
ChEMBL	CHEMBL367149 ✓
Properties	
Molecular formula	$C_{22}H_{32}O_2$
Molar mass	328.488 g/mol

Docosahexaenoic acid (**DHA**) is an omega-3 fatty acid. In chemical structure, DHA is a carboxylic acid with a 22-carbon chain and six *cis* double bonds; the first double bond is located at the third carbon from the omega end. Its trivial name is **cervonic acid**, its systematic name is ***all-cis*-docosa-4,7,10,13,16,19-hexa-enoic acid**, and its shorthand name is **22:6(n-3)** in the nomenclature of fatty acids.

Cold-water oceanic fish oils are rich in DHA. Most of the DHA in fish and complex organisms with access to cold-water oceanic foods originates in photosynthetic and heterotrophic microalgae, and becomes increasingly concentrated in organisms, as they move up the food chain. DHA is also commercially manufactured from microalgae; *Crypthecodinium cohnii* and another of the genus *Schizochytrium*. DHA manufactured using microalgae is vegetarian. Some animals with access to seafood make very little

DHA through metabolism, but obtain it in the diet. However, in strict herbivores, and carnivores that do not eat seafood, DHA is manufactured internally from α-linolenic acid, a shorter omega-3 fatty acid manufactured by plants (and also occurring in animal products as obtained from plants). Although α-linolenic acid (ALA) does convert to DHA, the process is inefficient and very limited even in healthy individuals. To obtain the benefits of DHA, consuming it directly yields most effective results.

DHA is metabolized to form the docosanoids, which comprise several families of potent hormones. DHA is a major fatty acid in sperm and brain phospholipids, particularly in the retina. Dietary DHA may reduce the risk of heart disease by reducing the level of blood triglycerides in humans. Low levels of DHA have been associated with Alzheimer's disease.

Central nervous system constituent

DHA is the most abundant omega-3 fatty acid in the brain and retina. DHA comprises 40% of the polyunsaturated fatty acids (PUFAs) in the brain and 60% of the PUFAs in the retina. 50% of the weight of a neuron's plasma membrane is composed of DHA.

Of all the fatty acids, DHA has the largest effect on brain PUFA composition. DHA is found in three phospholipids: phosphatidylethanolamine, ethanolamine plasmalogens, and phosphatidylserine (PS). It modulates the carrier-mediated transport of choline, glycine, and taurine, the function of delayed rectifier potassium channels, and the response of rhodopsin contained in the synaptic vesicles, among many other functions.

DHA deficiency is associated with cognitive decline. PS controls apoptosis, and low DHA levels lower neural cell PS and increase neural cell death. DHA is depleted in the cerebral cortex of severely depressed patients.

Metabolic synthesis

In the human body, DHA is either present in the diet or derived from eicosapentaenoic acid (EPA, 20:5, ω-3) via docosapentaenoic acid (DPA, 22:5 ω-3) as an intermediate. This had been thought to occur through an elongation step followed by the action of Δ4-desaturase. It is now more likely that DHA is biosynthesized via a C24 intermediate followed by beta oxidation in peroxisomes. Thus EPA is twice elongated yielding 24:5 ω-3, then desaturated to 24:6 ω-3, then shortened to DHA (22:6 ω-3) via beta oxidation. This pathway is known as **Sprecher's shunt**.

Health

Alzheimer's disease and decline of mental health

Docosahexaenoic acid in randomized trials did not slow decline of mental function in those with Alzheimer's disease. These trials were part of a large NIH (US National

Institutes of Health) intervention study to evaluate DHA in Alzheimer's disease. This is the first large scale human trial of DHA and Alzheimer's disease.

The NIA trial lasted 18 months and was conducted in people with mild to moderate Alzheimer's. Researchers from the National Institute on Aging (NIA)-supported Alzheimer's Disease Cooperative Study (ADCS), led by Joseph Quinn, MD, Associate Professor of Neurology at Oregon Health and Sciences University, conducted a double blind, randomized, placebo-controlled clinical trial comparing DHA and placebo in 402 people (average age=76) diagnosed with mild to moderate Alzheimer's at 51 sites in the U.S. According to the researchers, treatment with DHA clearly increased blood levels of DHA, and also appeared to increase brain DHA levels, based on a measured increase of DHA in study participants' cerebrospinal fluid (CSF).

However, DHA treatment did not slow the rate of change on tests of mental function (ADAS-cog), global dementia severity status (CDR-SOB), activities of daily living (ADL), or behavioral symptoms (NPI) in the study population as a whole. There was no different treatment effect between the mild and moderate Alzheimer's patients.

"These trial results do not support the routine use of DHA for patients with Alzheimer's," Quinn said.

Animal studies in the TG3 transgenic mouse model of Alzheimer's disease had linked decreases in amyloid plaques and tau to dietary DHA. Animal studies also showed that when combined with arachidonic acid (also present in fish oil), plaque formation was greater than without the arachidonic acid.

DHA deficiency likely plays a role in decline of mental function in healthy adults, this is indicated in a study from 2010 conducted at 19 U.S. clinical sites on 485 subjects aged 55 and older who met criteria for age-associated memory impairment found that DHA taken for six months improved memory and learning in healthy, older adults with mild memory complaints. These findings indicate the importance of early DHA intervention and provided a statistically significant benefit to cognitive function in aging individuals over 50 years of age.

Cancer

DHA was found to inhibit growth of human colon carcinoma cells, more than other omega-3 PUFAs. The cytotoxic effect of DHA wasn't caused by increased lipid peroxidation or any other oxidative damage, but rather decrease in cell growth regulators. However, different cancer lines handle PUFAs differently and display different sensitivities towards them. Such preliminary findings point to the need for further research and are not proof that DHA does or does not provide any benefit for intended treatment, cure, or mitigation of cancer. However, in 2008, DHA was shown to increase the efficacy of chemotherapy in prostate cancer cells, and in 2009, a chemoprotective effect in a mouse model was reported.

Pregnancy and lactation

DHA concentrations in breast milk range from 0.07% to greater than 1.0% of total fatty acids, with a mean of about 0.34%. DHA levels in breast milk are higher if a mother's diet is high in fish. The Food and Drug Administration has noted specific concerns for women who are pregnant, might become pregnant, nursing mothers, and young children regarding mercury levels in fish and shellfish.

DHA has recently gained attention as a supplement for pregnant women, noting studies of improved attention and visual acuity. One recent study indicates that low levels of plasma and erythrocyte DHA were associated with poor retinal development, low visual acuity, and poor cognitive development. In that same study, alpha-linolenic acid was shown as a source of fetal DHA, but that preformed DHA was more readily accredited. A working group from the ISSFAL (International Society for the Study of Fatty Acids and Lipids) recommended 300 mg/day of DHA for pregnant and lactating women, whereas the average consumption was between 45 mg and 115 mg per day of the women in the study. Other requirements are available from other sources.

DHASCO ("docosahexaenoic acid single cell oil") has been an ingredient in several brands of premium infant formula sold in North America since 2001 after Mead Johnson, the first infant formula manufacturer to add DHASCO and ARASCO (arachidonic acid single cell organism) to its Enfamil Lipil product, received a "Generally Regarded As Safe"status by the Food and Drug Administration and Health Canada.

DHASCO does not make infant formulas more like human milk than "conventional" formula containing Alpha-linolenic acid and linoleic acid, which are precursors to DHA. Formula sold in North America uses lipids from microorganisms grown in bioreactors as sources of DHA. There are no scientific review studies showing that DHA additives benefit brain development of term infants, as formula makers claim in their advertisements, which has led some public interest groups to file complaints with the Federal Trade Commission of the United States, alleging false and misleading advertising.

Nutrition

Promotion as a food additive

DHA is actively promoted by manufacturers as a food additive. Until recently, sales other than to makers of infant formula have been minimal; however, in 2007, several DHASCO-fortified dairy items (milk, yogurt) began selling in grocery stores.

There is less DHA available in the average diet than formerly, due to cattle being taken off grass and fed grain before butchering; likewise, there is less in eggs due to intensive farming. DHA is widely believed to be helpful to people with a history of heart disease, for premature infants, and to support healthy brain development especially in young

children. Some manufactured DHASCO is a vegetarian product extracted from algae. Both types are odorless and tasteless after processing.

Algae-derived DHA in infant nutrition

A study found that preterm infants fed baby formulas fortified with DHASCO provided better developmental outcomes than formulas not containing the supplement.

Studies of vegetarians and vegans

Vegetarian diets typically contain limited amounts of DHA, and vegan diets typically contain no DHA. Vegetarians and vegans have substantially lower levels of DHA in their body, and *short-term* supplemental ALA has been shown to increase EPA but not DHA. However, supplemental preformed DHA, available in algae-derived oils or capsules, has been shown to increase DHA levels. While there is little evidence of adverse health or cognitive effects due to DHA deficiency in adult vegetarians or vegans, fetal and breast milk levels remain a concern.

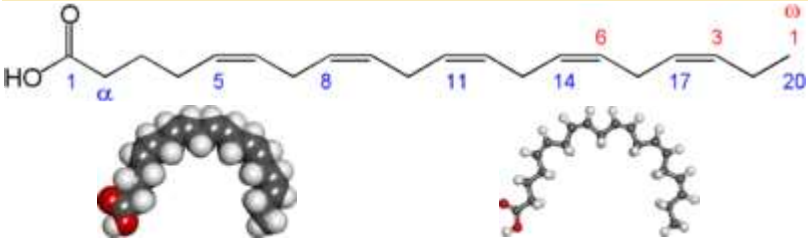
DHA and EPA in fish oils

Fish oil is widely sold in gelatin capsules containing a mixture of omega-3 fatty acids including EPA and smaller quantities of DHA. One study found that fish oil higher in DHA than EPA lowered inflammatory cytokines, such as IL-6 and IL-1β, associated with neurodegenerative and autoimmune diseases. They note that the brain normally contains DHA but no EPA, though both DHA and EPA plasma concentrations increased significantly for participants. One study of pure DHA supplementation on children with ADHD found no behavioral improvements, while another study found fish oil containing both EPA and DHA did improve behavior.

Hypothesized role in evolution

It has been suggested that the abundance of docosahexaenoic acid in seafood would have been helpful in the development of a large brain, though other researchers claim a terrestrial diet could also have provided the necessary docosahexaenoic acid.

Eicosapentaenoic acid

Eicosapentaenoic acid	
	
IUPAC name (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid	
Identifiers	
CAS number	10417-94-4 ✓
ChemSpider	393682 ✓
UNII	AAN7QOV9EA ✓
ChEMBL	CHEMBL460026 ✓
Properties	
Molecular formula	$C_{20}H_{30}O_2$
Molar mass	302.451 g/mol

Eicosapentaenoic acid (EPA or also icosapentaenoic acid) is an omega-3 fatty acid. In physiological literature, it is given the name 20:5(n-3). It also has the trivial name **timnodonic acid**. In chemical structure, EPA is a carboxylic acid with a 20-carbon chain and five *cis* double bonds; the first double bond is located at the third carbon from the omega end.

EPA is a polyunsaturated fatty acid (PUFA) that acts as a precursor for prostaglandin-3 (which inhibits platelet aggregation), thromboxane-3, and leukotriene-5 groups (all eicosanoids).

Sources

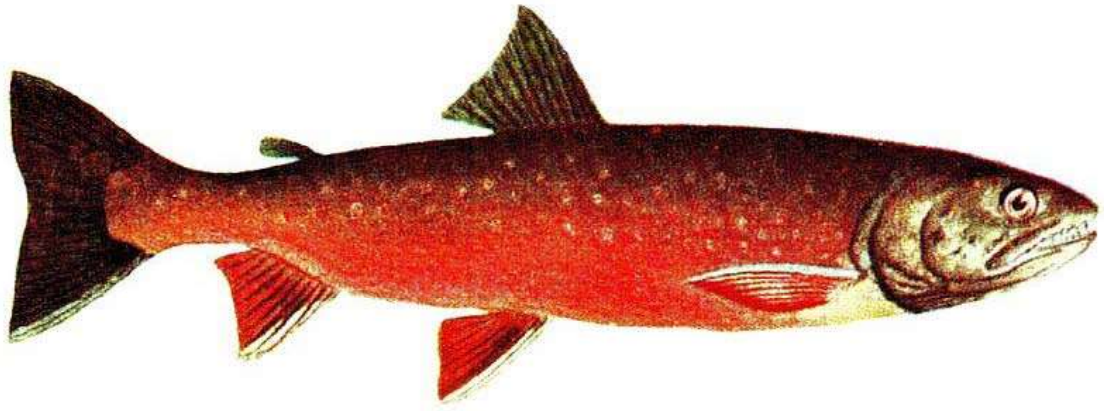
It is obtained in the human diet by eating oily fish or fish oil— e.g, cod liver, herring, mackerel, salmon, menhaden and sardine. It is also found in human breast milk.

However, fish do not naturally produce EPA, but obtain it from the algae they consume. It is available to humans from some non-animal sources (eg, commercially, from microalgae). Microalgae are being developed as a commercial source. EPA is not usually found in higher plants, but it has been reported in trace amounts in purslane. Microalgae, and supplements derived from it, are excellent alternative sources of EPA and other fatty acids, since fish often contain toxins due to pollution.

The human body can (and in case of a purely vegetarian diet often must, unless the aforementioned algae or supplements derived from them are consumed) also convert

alpha-linolenic acid (ALA) to EPA, but this is much less efficient than the resorption of EPA from food containing it, and ALA is itself an essential fatty acid, an appropriate supply of which must be ensured. Because EPA is also a precursor to docosahexaenoic acid (DHA), ensuring a sufficient level of EPA on a diet containing neither EPA nor DHA is harder both because of the extra metabolic work required to synthesize EPA and because of the use of EPA to metabolize DHA. Medical conditions like diabetes or certain allergies may significantly limit the human body's capacity for metabolization of EPA from ALA.

Clinical significance



Salmon is a rich source of EPA

The US National Institute of Health's MedlinePlus lists medical conditions for which EPA (alone or in concert with other ω-3 sources) is known or thought to be an effective treatment. Most of these involve its ability to lower inflammation.

Among omega-3 fatty acids, it is thought that EPA in particular may possess some beneficial potential in mental conditions, such as schizophrenia. Several studies report an additional reduction in scores on symptom scales used to assess the severity of symptoms, when additional EPA is taken.

Recent studies have suggested that EPA may affect depression, and importantly, suicidal behavior. One such study, took blood samples of 100 suicide-attempt patients and compared the blood samples to those of controls and found that levels of eicosapentaenoic acid were significantly lower in the washed red blood cells of the suicide-attempt patients.

EPA has inhibitory effect on CYP2C9 and CYP2C19 hepatic enzymes. At high dose, it may also inhibit the activity of CYP2D6 and CYP3A4, important enzymes involved in drug metabolism.

Research suggests that EPA improves the response of patients to chemotherapy, possibly by modulating the production of eicosanoid. It might also reduce the risk of developing certain types of cancer, including multiple myeloma.

Chapter- 18

Omega-3 Fatty Acid

***n*−3 fatty acids** (popularly referred to as **ω−3 fatty acids** or **omega-3 fatty acids**) are a family of essential unsaturated fatty acids that have in common a final carbon–carbon double bond in the *n*−3 position; that is, the third bond from the methyl end of the fatty acid.

Nutritionally important *n*−3 fatty acids include α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), all of which are polyunsaturated. The human body cannot synthesize *n*−3 fatty acids *de novo*, but it can form "long chain" 20-carbon *n*−3 fatty acids (like EPA) and 22-carbon *n*−3 fatty acids (like DHA) from the "short chain" eighteen-carbon *n*−3 fatty acid α-linolenic acid. The short chain *n*−3 fatty acids are converted to long chain forms (EPA, DHA) with an efficiency of approximately 5% in men, and at a greater percentage in women.

These conversions occur competitively with *n*−6 fatty acids, which are essential closely related chemical analogues that are derived from linoleic acid. Both the *n*−3 α-linolenic acid and *n*−6 linoleic acid must be obtained from food. Synthesis of the longer *n*−3 fatty acids from linolenic acid within the body is competitively slowed by the *n*−6 analogues. Thus accumulation of long-chain *n*−3 fatty acids in tissues is more effective when they are obtained directly from food or when competing amounts of *n*−6 analogs do not greatly exceed the amounts of *n*−3.

History

Although omega-3 fatty acids have been known as essential to normal growth and health since the 1930s, awareness of their health benefits has dramatically increased in the past few years. New versions of ethyl esterized omega-3 fatty acids, such as E-EPA and combinations of E-EPA and E-DHA, have drawn attention as highly purified and more effective products than the traditional ones. In the United States, these novel versions are often sold as prescription medications, such as Lovaza. In the European Union, they are available as dietary supplements.

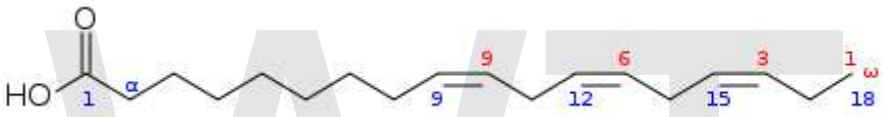
The health benefits of the long-chain omega-3 fatty acids — DHA and EPA omega-3 — are the best known. These benefits were discovered in the 1970s by researchers studying the Greenland Inuit Tribe. The Greenland Inuit people consumed large amounts of fat from seafood, but displayed virtually no cardiovascular disease. The high level of omega-

3 fatty acids consumed by the Inuit reduced triglycerides, heart rate, blood pressure, and atherosclerosis.

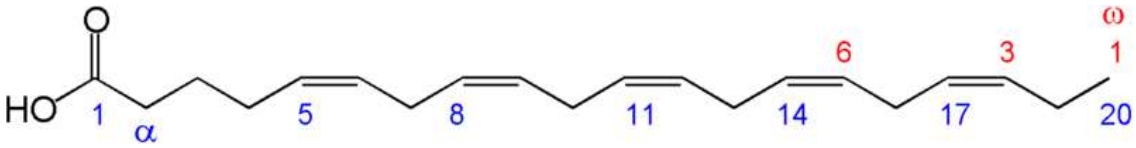
On September 8, 2004, the U.S. Food and Drug Administration gave "qualified health claim" status to EPA and DHA *n*−3 fatty acids, stating that "supportive but not conclusive research shows that consumption of EPA and DHA [*n*−3] fatty acids may reduce the risk of coronary heart disease." This updated and modified their health risk advice letter of 2001 (see below). Currently, regulatory agencies do not accept that there is sufficient evidence for any of the suggested benefits of DHA and EPA other than for cardiovascular health, and further claims should be treated with caution.

The Canadian Government has recognized the importance of DHA omega-3 and permits the following biological role claim for DHA: "DHA, an omega-3 fatty acid, supports the normal development of the brain, eyes and nerves."

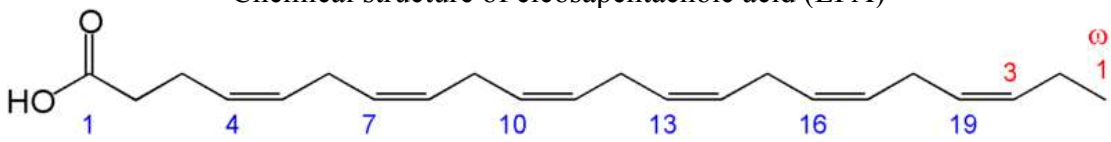
Chemistry



Chemical structure of alpha-linolenic acid (ALA), an essential *n*−3 fatty acid, (18:3Δ9c,12c,15c, which means a chain of 18 carbons with 3 double bonds on carbons numbered 9, 12 and 15). Although chemists count from the carbonyl carbon (Blue Numbering), physiologists count from the *n* (ω) carbon (red numbering). Note that from the *n* end (diagram right), the first double bond appears as the third carbon-carbon bond (line segment), hence the name "*n*−3". This is explained by the fact that the *n* end is almost never changed during physiologic transformations in the human body, as it is more stable energetically, and other carbohydrates compounds can be synthesized from the other carbonyl end, for example in glycerides, or from double bonds in the middle of the chain.



Chemical structure of eicosapentaenoic acid (EPA)



Chemical structure of docosahexaenoic acid (DHA)

The term ***n*−3** (also called **ω−3** or **omega-3**) signifies that the first double bond exists as the **third** carbon-carbon bond from the terminal methyl end (*n*) of the carbon chain.

n−3 fatty acids which are important in human nutrition are: α-linolenic acid (18:3, *n*−3; ALA), eicosapentaenoic acid (20:5, *n*−3; EPA), and docosahexaenoic acid (22:6, *n*−3; DHA). These three polyunsaturates have either 3, 5 or 6 double bonds in a carbon chain of 18, 20 or 22 carbon atoms, respectively. All double bonds are in the *cis*-configuration; in other words, the two hydrogen atoms are on the same side of the double bond.

Most naturally-produced fatty acids (created or transformed in animal or plant cells with an even number of carbon in chains) are in *cis*-configuration.

Like free oxygen radicals, iodine can add to double bonds of docosahexaenoic acid and arachidonic acid forming iodolipids.

List of *n*−3 fatty acids

This table lists several different names for the most common *n*−3 fatty acids found in nature.

Common name	Lipid name	Chemical name
n/a	16:3 (*n*−3)	*all-cis*-7,10,13-hexadecatrienoic acid
α-Linolenic acid (ALA)	18:3 (*n*−3)	*all-cis*-9,12,15-octadecatrienoic acid
Stearidonic acid (SDA)	18:4 (*n*−3)	*all-cis*-6,9,12,15-octadecatetraenoic acid
Eicosatrienoic acid (ETE)	20:3 (*n*−3)	*all-cis*-11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 (*n*−3)	*all-cis*-8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA)	20:5 (*n*−3)	*all-cis*-5,8,11,14,17-eicosapentaenoic acid
Docosapentaenoic acid (DPA), Clupanodonic acid	22:5 (*n*−3)	*all-cis*-7,10,13,16,19-docosapentaenoic acid
Docosahexaenoic acid (DHA)	22:6 (*n*−3)	*all-cis*-4,7,10,13,16,19-docosahexaenoic acid
Tetracosapentaenoic acid	24:5 (*n*−3)	*all-cis*-9,12,15,18,21-tetracosapentaenoic acid
Tetracosahexaenoic acid (Nisinic acid)	24:6 (*n*−3)	*all-cis*-6,9,12,15,18,21-tetracosahexaenoic acid

Biological significance

> *The biological effects of the* n−*3 are largely mediated by their interactions with the* n−*6 fatty acids.*

A 1992 article by biochemist William E.M. Lands provides an overview of the research into *n*−3 fatty acids, and is the basis of this section.

The 'essential' fatty acids were given their name when researchers found that they were essential to normal growth in young children and animals. (Note that the modern definition of 'essential' is more strict.) A small amount of *n*−3 in the diet (~1% of total calories) enabled normal growth, and increasing the amount had little to no additional effect on growth.

Likewise, researchers found that *n*−6 fatty acids (such as γ-linolenic acid and arachidonic acid) play a similar role in normal growth. However, they also found that *n*−6 was "better" at supporting dermal integrity, renal function, and parturition. These preliminary findings led researchers to concentrate their studies on *n*−6, and it was only in recent decades that *n*−3 has become of interest.

In 1964, it was discovered that enzymes found in sheep tissues converted *n*−6 arachidonic acid into the inflammatory agent called prostaglandin E_2 which both causes the sensation of pain and expedites healing and immune response in traumatized and infected tissues. By 1979, more of what are now known as eicosanoids were discovered: thromboxanes, prostacyclins and the leukotrienes. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from fatty acids and ending with metabolism by enzymes. However, if the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may have deleterious effects. Researchers found that certain *n*−3 fatty acids are also converted into eicosanoids, but at a much slower rate. Eicosanoids made from *n*−3 fatty acids are often referred to as anti-inflammatory, but in fact they are just less inflammatory than those made from *n*−6 fats. If both *n*−3 and *n*−6 fatty acids are present, they will "compete" to be transformed, so the ratio of long-chain *n*−3:*n*−6 fatty acids directly affects the type of eicosanoids that are produced.

This competition was recognized as important when it was found that thromboxane is a factor in the clumping of platelets, which can both cause death by thrombosis and prevent death by bleeding. The leukotrienes were similarly found to be important in immune/inflammatory-system response, and therefore relevant to arthritis, lupus, asthma, and recovery from infections. These discoveries led to greater interest in finding ways to control the synthesis of *n*−6 eicosanoids. The simplest way would be by consuming more *n*−3 and fewer *n*−6 fatty acids.

When administered as the ethyl ester, the omega-3 fatty acid EPA appears to form potent anti-inflammatory molecules, called resolvins and omega-3-oxylipins, which may partly explain the positive effects of fish oil.

The n-3 fatty acids DHA and EPA may act as direct ligands to a cell surface G-protein receptor affecting anti-inflammatory and insulin sensitization in mice.

Conversion efficiency of ALA to EPA and DHA

It has been reported that conversion of ALA to EPA and further to DHA in humans is limited, but varies with individuals. Women have higher ALA conversion efficiency than

men, probably due to the lower rate of utilization of dietary ALA for beta-oxidation. This suggests that biological engineering of ALA conversion efficiency is possible. Goyens *et al.* argue that it is the absolute amount of ALA, rather than the ratio of *n*−3 and *n*−6 fatty acids, which affects the conversion.

Potential health benefits

The 18 carbon α-linolenic acid has not been shown to have the same cardiovascular benefits as DHA or EPA. Currently there are many products on the market which claim to contain health promoting 'omega 3', but contain only α-linolenic acid (ALA), not EPA or DHA. These products contain mainly plant oils and must be converted by the body to create DHA and are therefore considered less efficient. DHA and EPA are made by microalgae that live in seawater. These are then consumed by fish and accumulate to high levels in their internal organs. The Environmental Protection agency has issued a fish consumption advisory due to potential toxic mercury levels in fish. DHA also can be produced directly from microalgae to provide a vegetarian source.

People with certain circulatory problems, such as varicose veins, may benefit from such supplements containing EPA and DHA which stimulate blood circulation, increase the breakdown of fibrin, a compound involved in clot and scar formation, and additionally have been shown to reduce blood pressure. There is scientific evidence that *n*−3 fatty acids reduce blood triglyceride levels and regular intake may reduce the risk of secondary and primary heart attack.

Some potential benefits have been reported in conditions such as rheumatoid arthritis and cardiac arrhythmias.

There is preliminary evidence that *n*-3 fatty acids supplementation might be helpful in cases of depression and anxiety. Studies report improvement from *n*-3 fatty acids supplementation alone and in conjunction with medication. The *New York Times* reports that at least one study, however, has found no connection between depression in heart patients and supplements containing *n*-3 fatty acids.

Some research suggests that fish oil intake may reduce the risk of ischemic and thrombotic stroke, although large amounts may actually increase the risk of hemorrhagic stroke (see below): lower amounts are not related to this risk, 3 grams of total EPA/DHA daily are generally recognized as safe (GRAS) with no increased risk of bleeding involved and many studies used substantially higher doses without major side effects (for example: 4.4 grams EPA/2.2 grams DHA in 2003 study). A systematic review of recent studies found evidence that alpha-linolenic acid does not confer the health benefits of *n*−3 fatty acids derived from wild fish sources.

Cancer

Several studies report possible anti-cancer effects of *n*−3 fatty acids (particularly breast, colon, and prostate cancer). Omega-3 fatty acids reduced prostate tumor growth, slowed

histopathological progression, and increased survival. Among n-3 fatty acids [omega-3], neither long-chain nor short-chain forms were consistently associated with breast cancer risk. High levels of docosahexaenoic acid, however, the most abundant n-3 PUFA in erythrocyte membranes, were associated with a reduced risk of breast cancer. A 2006 report in the Journal of the American Medical Association concluded that their review of literature covering cohorts from many countries with a wide variety of demographic concluded that there was no link between *n*−3 fatty acids and cancer. This is similar to the findings of a review by the British Medical Journal of studies up to February 2002 that failed to find clear effects of long and shorter chain *n*−3 fats on total mortality, combined cardiovascular events and cancer.

A 2007 systematic review of n-3 fatty acids and cachexia found evidence that oral n-3 fatty acid supplements benefit cancer patients, improving appetite, weight and quality of life. A 2009 trial found that a supplement of eicosapentaenoic acid helped cancer patients retain muscle mass.

Cardiovascular disease

In 1999, the GISSI-Prevenzione Investigators reported in the Lancet, the results of major clinical study in 11,324 patients with a recent myocardial infarction. Treatment 1 gram per day of *n*−3 fatty acids reduced the occurrence of death, cardiovascular death and sudden cardiac death by 20%, 30% and 45% respectively. These beneficial effects were seen from three months onwards.

In April 2006, a team led by Lee Hooper at the University of East Anglia in Norwich, UK, published a review of almost 100 separate studies of *n*−3 fatty acids found in abundance in oily fish. It concluded that they do not have a significant protective effect against cardiovascular disease. This meta-analysis was controversial and stands in stark contrast with two different reviews also performed in 2006 by the American Journal of Clinical Nutrition and a second JAMA review that both indicated decreases in total mortality and cardiovascular incidents (i.e. myocardial infarctions) associated with the regular consumption of fish and fish oil supplements.

In the March 2007 edition of the journal *Atherosclerosis*, 81 Japanese men with unhealthy blood sugar levels were randomly assigned to receive 1800 mg daily of eicosapentaenoic acid (EPA) with the other half being a control group. The thickness of the carotid arteries and certain measures of blood flow were measured before and after supplementation. This went on for approximately two years. A total of 60 patients (30 in the E-EPA group and 30 in the control group) completed the study. Those given the EPA had a statistically significant decrease in the thickness of the carotid arteries along with improvement in blood flow. The authors indicated that this was the first demonstration that administration of purified EPA improves the thickness of carotid arteries along with improving blood flow in patients with unhealthy blood sugar levels.

A study found in *Clinical Cardiology* in 2009 shows that *n*-3 prevents monocytes from adhering to arterial walls and contributing to plaque build-up. This is done by reducing thromboxane A2, a chemical that promotes clotting and causes vasoconstriction.

In a study published in the American Journal of Health System Pharmacy March 2007, patients with high triglycerides and poor coronary artery health were given 4 grams a day of a combination of EPA and DHA along with some monounsaturated fatty acids. Those patients with very unhealthy triglyceride levels (above 500 mg/dl) reduced their triglycerides on average 45% and their VLDL cholesterol by more than 50%. VLDL is a bad type of cholesterol and elevated triglycerides can also be deleterious for cardiovascular health.

A study on the benefits of EPA published in *The Lancet* in March 2007, involved over 18,000 patients with unhealthy cholesterol levels. The patients were randomly assigned to receive either 1,800 mg a day of E-EPA with a statin drug or a statin drug alone. The trial went on for a total of five years. It was found at the end of the study those patients in the E-EPA group had superior cardiovascular function. Non-fatal coronary events were also significantly reduced in the E-EPA group. The authors concluded that EPA is a promising treatment for prevention of major coronary events, especially non-fatal coronary events.

Similar to those who follow a Mediterranean diet, Arctic-dwelling Inuit - who consume high amounts of *n*−3 fatty acids from fatty fish - also tend to have higher proportions of *n*−3, increased HDL cholesterol and decreased triglycerides (fatty material that circulates in the blood) and less heart disease. Eating walnuts (the ratio of *n*−3 to *n*−6 is circa 1:4 respectively) was reported to lower total cholesterol by 4% relative to controls when people also ate 27% less cholesterol.

A study carried out involving 465 women showed serum levels of eicosapentaenoic acid is inversely related to the levels of anti-oxidized-LDL antibodies. Oxidative modification of LDL is thought to play an important role in the development of atherosclerosis.

A study shows that survivors of past myocardial infarctions are less likely to die from an arrhythmic event if they are consuming high levels of *n*-3. It is possible that these anti-arrhythmic effects are due to *n*-3 fatty acid's ability to increase the fibrillation threshold of the heart tissue.

A study shows that *n*-3 fatty acids have mild anti-hypertensive effects. When subjects consumed *n*-3 from oily fish on a regular basis, their systolic blood pressure was lowered by about 3.5-5.5 mmHg.

Immune function

In a study regarding fish oil published in the *Journal of Nutrition* in April 2007, sixty four healthy Danish infants from nine to twelve months of age received either cow's milk or infant formula alone or with fish oil. It was found that those infants supplemented with

fish oil had improvement in immune function maturation with no apparent reduction in immune activation.

Neurology

Limited evidence suggests that long-chain *n*-3 fatty acids delay or prevent the progression of certain psychotic disorders in high-risk children and adolescents. The evidence included the observation that individuals diagnosed with schizophrenia exhibited reduced levels of both *n*-6 and *n*-3 polyunsaturated fatty acids, and the results of a study in which the treatment of high-risk children with a dietary supplement containing both eicosapentaenoate and docosahexaenoate produced a statistically significant (95% confidence, but not 97.5% confidence) decrease in progression to schizophrenia.

Consumption of ethyl eicosapentaenoate (E-EPA) partially countered memory impairment in a rat model of Alzheimer's disease and produced a statistically insignificant decrease in human depression.

Fish oil has been shown to have no effect on cognitive performance in older individuals (65 years of age or older) without dementia.

Inflammation

Although not confirmed as an approved health claim, current research suggests that the antiinflammatory activity of long-chain *n*−3 fatty acids may translate into clinical effects. For example, there is evidence that rheumatoid arthritis sufferers taking long-chain *n*−3 fatty acids from sources such as fish have reduced pain compared to those receiving standard NSAIDs.

Risks

Health risks

Non-cardiac health risks

In a letter published October 31, 2000, the United States Food and Drug Administration Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements noted that known or suspected risks of EPA and DHA consumed in excess of 3 grams per day may include the possibility of:

- Increased incidence of bleeding.
- Hemorrhagic stroke.
- Oxidation of omega-3 fatty acids forming biologically active oxidation products.
- Increased levels of low density lipoproteins (LDL) cholesterol or apoproteins associated with LDL cholesterol among diabetics and hyperlipidemics.
- Reduced glycemic control among diabetics.

Subsequent advice from the FDA and national counterparts have permitted health claims associated with heart health.

Cardiac risk

Persons with congestive heart failure, chronic recurrent angina pectoris or evidence that their heart is receiving insufficient blood flow are advised to talk to their doctor before taking *n*−3 fatty acids. There have been concerns if such persons take *n*−3 fatty acids or eating foods that contain them in substantial amounts. In a recent large study, *n*−3 fatty acids on top of standard heart failure therapy produced a small but statistically significant benefit in terms of mortality and hospitalization.

In congestive heart failure, cells that are only barely receiving enough blood flow become electrically hyperexcitable. This, in turn, can lead to increased risk of irregular heartbeats, which, in turn, can cause sudden cardiac death. *n*−3 fatty acids seem to stabilize the rhythm of the heart by effectively preventing these hyperexcitable cells from functioning, thereby reducing the likelihood of irregular heartbeats and sudden cardiac death. For most people, this is beneficial and could account for most of the large reduction in the likelihood of sudden cardiac death. Nevertheless, for people with congestive heart failure, the heart is barely pumping blood well enough to keep them alive. In these patients, *n*−3 fatty acids may eliminate enough of these few pumping cells that the heart would no longer be able to pump sufficient blood to live, causing an increased risk of cardiac death.

The n−*6 to* n−*3 ratio*

Clinical studies indicate that the ingested ratio of *n*−6 to *n*−3 (especially linoleic vs alpha-linolenic) fatty acids is important to maintaining cardiovascular health. However, two studies published in 2005 and 2007 found that while *n*−3 polyunsaturated fatty acids are extremely beneficial in preventing heart disease in humans, the levels of *n*−6 polyunsaturated fatty acids (and therefore the ratios) were insignificant.

Both *n*−3 and *n*−6 fatty acids are essential, i.e. humans must consume them in the diet. *n*−3 and *n*−6 eighteen-carbon polyunsaturated faty acids compete for the same metabolic enzymes, thus the *n*−6:*n*−3 ratio will significantly influence the ratio of the ensuing eicosanoids (hormones), (e.g. prostaglandins, leukotrienes, thromboxanes etc.), and will alter the body's metabolic function. Generally, grass-fed animals accumulate more *n*−3 than do grain-fed animals which accumulate relatively more *n*−6. Metabolites of *n*−6 are more inflammatory (esp. arachidonic acid) than those of *n*−3. This necessitates that *n*−3 and *n*−6 be consumed in a *balanced proportion*; healthy ratios of *n*−6:*n*−3 range from 1:1 to 1:4 (an individual ideally needs more *n*−3 than *n*−6.) Studies suggest that the evolutionary human diet, rich in game animals, seafood and other sources of *n*−3, may have provided such a ratio.

Typical Western diets provide ratios of between 10:1 and 30:1 - i.e., dramatically higher levels of *n*−6 polyunsaturated fatty acids. Here are the ratios of *n*−6 to *n*−3 fatty acids in some common vegetable oils: canola 2:1, soybean 7:1, olive 3–13:1, sunflower (no *n*−3),

flax 1:3, cottonseed (almost no *n*−3), peanut (no *n*−3), grapeseed oil (almost no *n*−3) and corn oil 46:1 ratio of *n*−6 to *n*−3.

Research frontiers

Developmental differences

Although not supported by current scientific evidence as a primary treatment for ADHD, autism spectrum disorders, and other developmental differences, omega-3 fatty acids have gained popularity for children with these conditions. A 2004 Internet survey found that 29% of surveyed parents used essential fatty acid supplements to treat children with autistic spectrum disorders.

Omega-3 fatty acids offer a promising complementary approach to standard treatments for ADHD and developmental coordination disorder. Fish oils appear to reduce ADHD-related symptoms in some children. Double blind studies have showed "medium to strong treatment effects of omega 3 fatty acids on symptoms of ADHD" after administering amounts around 1 gram for three to six months.

A 2009 survey concluded that there is not enough scientific evidence to support the effectiveness of omega-3 fatty acids for autism spectrum disorders. One randomized controlled trial found that omega-3 fatty acids did not significantly affect aberrant behavior in autistic children, and although the investigators noted reduced hyperactivity, their later reanalysis reported that the reduction was not statistically significant.

Low birth weight

In a study of nearly 9,000 pregnant women, researchers found women who ate fish once a week during their first trimester had 3.6 times less risk of low birth weight and premature birth than those who ate no fish. Low consumption of fish was a strong risk factor for preterm delivery and low birth weight. However, attempts by other groups to reverse this increased risk by encouraging increased pre-natal consumption of fish were unsuccessful.

Psychiatric disorders

n−3 fatty acids are thought by some to have membrane-enhancing capabilities in brain cells. One medical explanation is that *n*−3 fatty acids play a role in the fortification of the myelin sheaths. Not coincidentally, *n*−3 fatty acids comprise approximately eight percent of the average human brain according to Dr. David Horrobin, a pioneer in fatty acid research. Ralph Holman of the University of Minnesota, another major researcher studying essential fatty acids, who gave omega-3 its name, surmised how *n*−3 components are analogous to the human brain by stating that "DHA is structure, EPA is function."

A benefit of *n*−3 fatty acids is helping the brain to repair damage by promoting neuronal growth. In a six-month study involving people with schizophrenia and Huntington's

disease who were treated with E-EPA or a placebo, the placebo group had clearly lost cerebral tissue, while the patients given the supplements had a significant increase of grey and white matter.

In the prefrontal cortex (PFC) of the brain, low brain *n*−3 fatty acids are thought to lower the dopaminergic neurotransmission, possibly contributing to the negative and neurocognitive symptoms in schizophrenia. This reduction in dopamine system function in the PFC may lead to an overactivity in dopaminergic function in the limbic system of the brain which is suppressively controlled by the PFC dopamine system, causing the positive symptoms of schizophrenia. This is called the *n*−3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia (Ohara, 2007). This mechanism may explain why *n*−3 supplementation shows effects against both positive, negative and cognitive symptoms in schizophrenia.

Consequently, the past decade of *n*−3 fatty acid research has procured *some* Western interest in *n*−3 fatty acids as being a legitimate 'brain food.' Still, recent claims that one's intelligence quotient, psychological tests measuring certain cognitive skills, including numerical and verbal reasoning skills, are increased on account of *n*−3 fatty acids consumed by pregnant mothers remain unreliable and controversial. An even more significant focus of research, however, lies in the role of *n*−3 fatty acids as a non-prescription treatment for certain psychiatric and mental diagnoses and has become a topic of much research and speculation. A 2011 report of preliminary research on mice found that omega-3 deficiency was linked to depression and mood disorders.

In 1998, Andrew L. Stoll, MD and his colleagues at Harvard University conducted a small double-blind placebo-controlled study in thirty patients diagnosed with bipolar disorder. Most subjects in this study were already undergoing psychopharmacological treatment (e.g. 12 out of the 30 were taking lithium). Over the course of four months, he gave 15 subjects capsules containing olive oil, and another 15 subjects capsules containing nine grams of pharmaceutical-quality EPA and DHA. The study showed that subjects in the *n*−3 group were less likely to experience a relapse of symptoms in the four months of the study. Moreover, the *n*−3 group experienced significantly more recovery than the placebo group. However, a commentary on the Stoll study notes that the improvement in the *n*−3 group was too small to be clinically significant. Though Stoll believes that the 1999 experiment was not as optimal as it could have been and has accordingly pursued further research, the foundation has been laid for more researchers to explore the theoretical association between absorbed *n*−3 fatty acids and signal transduction inhibition in the brain.

"Several epidemiological studies suggest covariation between seafood consumption and rates of mood disorders. Biological marker studies indicate deficits in omega−3 fatty acids in people with depressive disorders, while several treatment studies indicate therapeutic benefits from omega-3 supplementation. A similar contribution of omega-3 fatty acids to coronary artery disease may explain the well-described links between coronary artery disease and depression. Deficits in omega-3 fatty acids have been identified as a contributing factor to mood disorders and offer a potential rational

treatment approach." In 2004, a study found that 100 suicide attempt patients on average had significantly lower levels of EPA in their blood as compared to controls.

In 2006 the Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association (APA) stated the following: "The preponderance of epidemiologic and tissue compositional studies supports a protective effect of omega-3 EFA intake, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in mood disorders. Meta-analyses of randomized controlled trials demonstrate a statistically significant benefit in unipolar and bipolar depression (p=.02). The results were highly heterogeneous, indicating that it is important to examine the characteristics of each individual study to note the differences in design and execution. There is less evidence of benefit in schizophrenia. EPA and DHA appear to have negligible risks and some potential benefit in major depressive disorder and bipolar disorder, but results remain inconclusive in most areas of interest in psychiatry. Health benefits of omega-3 EFA may be especially important in patients with psychiatric disorders, due to high prevalence rates of smoking and obesity and the metabolic side effects of some psychotropic medications."

Another meta-analysis published in the Journal of Clinical Psychiatry in 2007, based on 10 clinical trials, found that Omega-3 polyunsaturated fatty acids significantly improved depression in patients with both unipolar and bipolar disorder. However, based upon the heterogeneity of the trials, the authors concluded that "more large-scale, well-controlled trials are needed to find out the favorable target subjects, therapeutic dose of EPA and the composition of omega-3 PUFAs in treating depression". A small American trial, published in 2009, concluded that E-EPA, as monotherapy, demonstrated a statistically insignificant advantage over placebo, possibly due to study limitations.

Dietary sources

Daily values

As macronutrients, fats are not assigned recommended daily allowances. Macronutrients have AI (acceptable intake) and AMDR (acceptable macronutrient distribution range) instead of RDAs. The AI for *n*−3 is 1.6 grams/day for men and 1.1 grams/day for women while the AMDR is 0.6% to 1.2% of total energy.

A growing body of literature suggests that higher intakes of α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) may afford some degree of protection against coronary heart disease. Because the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all *n*−3 fatty acids. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA." There was insufficient evidence as of 2005 to set a UL (upper tolerable limit) for *n*−3 fatty acids.

A perceived risk of fish oil *n*−3 supplementation has been heavy metal poisoning by the body's accumulation of traces of heavy metals, in particular mercury, lead, nickel, arsenic

and cadmium as well as other contaminants (PCBs, furans, dioxins, PBDEs), which potentially might be found especially in less-refined fish oil supplements. However, in reality, heavy metal toxicity from consuming fish oil supplements is highly unlikely. This is because heavy metals selectively bind with protein in the fish flesh rather than accumulate in the oil. An independent test in 2006 of 44 fish oils on the US market found that all of the products passed safety standards for potential contaminants. The FDA recommends that total dietary intake of *n*−3 fatty acids from fish not exceed 3 grams per day, of which no more than 2 grams per day are from nutritional supplements.

Historically, the Council for Responsible Nutrition (CRN) and the World Health Organization (WHO) have published acceptable standards regarding contaminants in fish oil. The most stringent current standard is the International Fish Oils Standard (IFOS). Fish oils that typically make this highest grade are those that are molecularly distilled under vacuum, and have virtually no measurable level of contaminants (measured parts per billion and parts per trillion).

n−3 supplementation in food has been a significant recent trend in food fortification, with global food companies launching *n*−3 fortified bread, mayonnaise, pizza, yogurt, orange juice, children's pasta, milk, eggs, confections and infant formula.

The American Heart Association has set up dietary recommendations for *n*-3 due to its cardiovascular benefits. According to the AHA, individuals with no history of coronary heart disease or myocardial infarction should consume oily fish or fish oils two times per week. Those who have been diagnosed with coronary heart disease after infarction should consume 1 g EPA and DHA per day from oily fish or supplements. Individuals who wish to lower blood triglycerides should consume 2-4 g of EPA and DHA per day in the form of supplements.

Fish

The most widely available dietary source of EPA and DHA is cold water oily fish such as salmon, herring, mackerel, anchovies and sardines, which they obtain from consumption of algae. Oils from these fish have a profile of around seven times as much *n*−3 as *n*−6. Other oily fish such as tuna also contain *n*−3 in somewhat lesser amounts. Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants like PCBs and dioxin, which are known to accumulate up the food chain. After extensive review, researchers from Harvard's School of Public Health reported in the *Journal of the American Medical Association* (2006) that the benefits of fish intake generally far outweigh the potential risks. As fish oil supplements are bought for their healthful Omega-3 fatty acid content, it is therefore vital that manufacturers and suppliers of these products ensure that they do not contain high levels of dioxins and other toxins.

Not all forms of fish oil may be equally digestible. Of four studies that compare bioavailability of the glyceryl ester form of fish oil vs. the ethyl ester form, two have concluded that the natural glyceryl ester form is better, and the other two studies did not

find a significant difference. No studies have shown the ethyl ester form to be superior, although it is cheaper to manufacture.

Although fish is a dietary source of *n*−3 fatty acids, fish do not synthesize them; they obtain them from the algae (microalgae in particular) or plankton in their diet.

Grams of *n*−3 per 3oz (85g) serving of popular fish.,

Common name	grams *n*−3
Tuna	0.21–1.1
Tuna (canned, light)	0.17-0.24
Pollock	0.45
Salmon	1.1–1.9
Cod	0.15–0.24
Catfish	0.22–0.3
Flounder	0.48
Grouper	0.23
Halibut	0.60–1.12
Mahi mahi	0.13
Orange roughy	0.028
Red snapper	0.29
Shark	0.83
Swordfish	0.97
Tilefish	0.90
King mackerel	0.36
Greenshell/lipped mussels	0.950
Hoki (Blue grenadier)	0.410
Gemfish	0.400
Blue eye cod	0.310
Sydney rock oysters	0.300
Tuna canned	0.230
Snapper	0.220
Eggs, large regular	0.109
Barramundi saltwater	0.100
Giant tiger prawn	0.100
Lean red meat	0.031
Turkey	0.030
Cereals, rice, pasta, etc.	0
Fruit	0
Milk regular	0
Regular bread	0

Vegetables	0
Vegetable oils & spreads	0

Krill

Krill oil is a newly discovered source of *n*−3 fatty acids. Various claims are made in support of krill oil as a superior source of *n*−3 fatty acids. It was recently demonstrated that effect of krill oil is similar to fish oil, but at a lower dose of EPA and DHA.

Green-lipped mussel

Green-lipped mussel from New Zealand also known as *Perna canaliculus* is another source of *n*-3 fatty acids. Research suggests that green-lipped mussels contain a distinct blend of *n*-3 fatty acids in comparison to other sources of *n*-3s. Most published studies report green-lipped mussels' health benefits with inflammation. The book *The Inflammation Revolution* by George Halpern, MD., PhD., professor at Hong Kong Polytechnic University discusses the effects of green-lipped mussels in comparison to NSAIDs in the treatment of inflammatory conditions, particularly arthritis. Lyprinol is a patented New Zealand mussel oil extract.

Plant sources

Flax seeds produce linseed oil, which has a very high ALA content

Please note that these tables are incomplete and also show the ALA content of nuts, not the DHA or EPA content.

Table 1. ALA content as the percentage of *n*−3 in the seed oil.

Common name	Alternative name	Linnaean name	% *n*−3
Perilla	shiso	*Perilla frutescens*	61
Chia	chia sage	*Salvia hispanica*	58
Flax	linseed	*Linum usitatissimum*	55
Lingonberry	Cowberry	*Vaccinium vitis-idaea*	49
Camelina	Gold-of-pleasure	*Camelina sativa*	36
Purslane	Portulaca	*Portulaca oleracea*	35
Black Raspberry		*Rubus occidentalis*	33
Hemp		*Cannabis Sativa*	19

Table 2. ALA content as the percentage of *n*−3 in the whole food.

Common name	Linnaean name	% *n*−3
Flaxseed	*Linum usitatissimum*	18.1
Butternuts	*Juglans cinerea*	8.7
Hempseed	*Cannabis sativa*	8.7
Persian Walnuts	*Juglans regia*	6.3
Pecan nuts	*Carya illinoinensis*	0.6
Hazel nuts	*Corylus avellana*	0.1

Six times richer than most fish oils in *n*−3, albeit in the short chain form lacking EPA and DHA, flax (or linseed) (*Linum usitatissimum*) and its oil are perhaps the most widely available botanical source of *n*−3. Flaxseed oil consists of approximately 55% alpha-linolenic acid (ALA). Flax, like *Salvia hispanica* (chia), contains approximately three times as much *n*−3 as *n*−6. However, the Center for Science in the Public Interest reports "the omega-3s that FDA considers healthful (DHA and EPA) are not found in plants such as flax seed [but rather, ALA is]."

Purslane contains more Omega-3 fatty acids (alpha-linolenic acid in particular) than any other leafy vegetable plant. Purslane has .01 mg/g of Eicosapentaenoic acid (EPA) and this is an extraordinary amount of EPA for vegetable sources.

Eggs

Eggs produced by chicken fed a diet of greens and insects produce higher levels of *n*−3 fatty acids (mostly ALA) than chicken fed corn or soybeans. In addition to feeding chickens insects and greens, fish oils may be added to their diet to increase the amount of fatty acid concentrations in eggs. The addition of flax and canola seeds to the diet of

chickens, both good sources of alpha-linolenic acid, increases the omega-3 content of the eggs. However, the Center for Science in the Public Interest reports that "the omega-3s that FDA considers healthful (DHA and EPA) are not found in plants such as flax seed." It also reports that "Eggs contain too much saturated fat and cholesterol to meet FDA's definition of healthy." The addition of green algae or seaweed to the diet boosts the content of DHA and EPA omega-3 content, which are the forms of omega-3 that are approved by the FDA for medical claims. A common consumer complaint is that "Omega-3 eggs can sometimes have a fishy taste if the hens are fed marine oils."

Meat

The *n*−6 to *n*−3 ratio of grass-fed beef is about 2:1, making it a more useful source of *n*−3 than grain-fed beef, which usually has a ratio of 4:1.

In most countries, commercially available lamb is typically grass-fed, and thus higher in *n*−3 than other grain-fed or grain-finished meat sources. In the United States, lamb is often finished (i.e. fattened before slaughter) with grain, resulting in lower *n*−3.

The omega-3 content of chicken meat may be enhanced by increasing the animals' dietary intake of grains that are high in *n*−3, such as flax, chia, and canola.

Kangaroo meat is also a source of *n*−3 with fillet and steak containing 74 mg per 100g of raw meat.

Seal oil

Seal oil is a source of EPA, DPH, and DPA. According to Health Canada, it helps to support the development of the brain, eyes and nerves in children up to 12 years of age. However, like all seal products, it is not allowed for import into the European Union

Other sources

Milk and cheese from grass-fed cows may also be good sources of *n*−3. One UK study showed that half a pint of milk provides 10% of the recommended daily intake (RDI) of ALA, while a piece of organic cheese the size of a matchbox may provide up to 88%".

The microalgae *Crypthecodinium cohnii* and *Schizochytrium* are rich sources of DHA (22:6 *n*−3) and can be produced commercially in bioreactors. This is the only source of DHA acceptable to vegans. Oil from brown algae (kelp) is a source of EPA. Persian Walnuts are one of few nuts that contain appreciable *n*−3 fat, with approximately a 1:4 ratio of *n*−3 to *n*−6. Acai palm fruit also contains *n*−3 fatty acids.