food supplements europe

Facts about vitamins, minerals and other food components with health effects

How we live and what we eat receives greater attention today than ever before.

CONTENTS

VITAMINS

VITAMIN A

Vitamin A is an essential fat-soluble micronutrient. The term vitamin A describes a group of compounds related to retinol. Preformed vitamin A is found in foods of animal origin and food supplements only. Some carotenoids found in foods of plant origin (α-carotene, β-carotene, β-cryptoxanthine) can be converted to vitamin A by an enzymatic process. Conversion is regulated by the body's vitamin A status. Foods can be fortified with preformed vitamin A or provitamin-A carotenoids.

Vitamin A activity is measured in Retinol Equivalents (RE). 1 mg RE = 1 mg retinol (3.33 IU vitamin A, 6 mg β-carotene, 12 mg other provitamin-A carotenoids). Newer data indicate that, to produce 1 mg retinol from fruits and vegetables, more than twice this amount of carotenoids may be needed.

Importance for health[1,2]

Vitamin A is essential for vision, growth and development, and immune function.

Vision

Receptor cells in the retina of the eye contain a light-sensitive pigment called visual purple (rhodopsin). When exposed to light, the pigment disintegrates into its components (a protein called opsin and a vitamin A metabolite called retinal) and releases electrical stimuli to the brain to form the picture that we see. To maintain vision, new rhodopsin must be continuously formed using vitamin A. One of the earliest signs of a poor vitamin A status is 'night blindness' (difficulty to see in dim light).

Another form of vitamin A (retinoic acid) is needed to maintain the proper functioning of the cornea (the transparent fibrous front layer of the eyeball) and the conjunctiva (the mucous membrane that nurtures and protects the front of the eye).

Growth and development

Vitamin A is important for the proper functioning of most organs in the body, because it is involved in the genetic regulation of cell formation and differentiation, and in intercellular communication. It is needed for reproduction and for the proper development of the foetus in the womb. Both too little and too much vitamin A can result in malformation of the skeleton, nervous system, heart, eyes and ears. The integrity of epithelial cells throughout the body (skin, gut, heart, lungs, bladder, eyes, etc.) is dependent on an adequate supply of vitamin A. When it is lacking, epithelial cells stop producing mucous, and "dry out".

Immune function

Vitamin A helps to protect against infections in a number of ways. It ensures the effectiveness of the mechanical barriers (skin and mucous membranes), and increases the production and efficacy of protective cells, such as phagocytes (that engulf "foreign" particles), killer cells and lymphocytes (that produce antibodies and other molecules to fight against intruders).

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of vitamin A (including β-carotene) as a basis for health claims:[3,4]

- Normal cell differentiation
- Normal function of the immune system
- Maintenance of normal skin and mucous membranes
- Maintenance of normal vision
- Normal metabolism of iron

Food sources

The richest food source of preformed vitamin A is liver; less than 5 g covers the daily requirement, putting people who regularly consume liver at a high risk of overconsumption. Appreciable quantities of preformed vitamin A are found in whole milk, butter, eggs and cheese. Carrots, spinach and broccoli are good sources of provitamin-A carotenoids when appropriately processed and cooked.

Vitamin A is essential for vision, growth and development, and immune function.

Vitamin A is sensitive to light and heat, especially in the presence of oxygen, and in an alkaline environment.During storage and cooking, appreciable amounts can be lost. Approximately, 21-29% of vitamin A intake is provided by vegetables, 14-16% from milk and around 10% from meats excluding liver[6] (Table 1).

Table 1: Food sources of vitamin A[5]

Food	Serving	% of average daily dietary requirements provided by one serving
Liver (beef)	100 g	950
Egg	1 (50 g)	10
Milk (whole)	250 ml	4
Butter	15 g	12
Cheese (Cheddar)	50 g	18
Salmon	100 g	5
Carrots (cooked)	100 g	100
Spinach (cooked)	100 g	65
Broccoli (cooked)	100 g	14
Melon (cantaloupe)	100 g	20

Food supplements

Food supplements sold in Europe generally contain a daily dosage of between 400 and 1500 µg. The forms of vitamin A most commonly used in vitamin supplements are retinyl acetate, retinyl palmitate and retinol.

In Ireland, food supplements provide between 5 and 8% of total intake of vitamin A.[7] In the UK, dietary supplements containing vitamin A increased mean daily intake by 12% for men and 19% for women. Supplements made the greatest contribution to total intake in women aged 19 to 24 years with a 26% increase over intake from food sources. The highest average daily intake of vitamin A from food supplements was 656 µg RE in women aged between 35 and 49 years (at the 97.5 percentile).[7]

Food fortification

In many countries in Europe the law requires the addition of vitamin A to margarine, and in some cases it is routinely added to other fat spreads. It is widely viewed that the addition of vitamin A to 'butter replacers' and other foods where the fat and hence the vitamin A has been at least partially removed is important for maintaining the vitamin A status of certain groups of the population, for example, the elderly. Vitamin A is added as beta-carotene (provitamin A) to a range of foods, primarily to juice based drinks. In accordance with EU legislation vitamin A is required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

VITAMIN A

Table 2: Recommended dietary allowances (RDA) of vitamin A (µg retinol equivalents) for men[8]

Country	Men
Belgium, 2009	600
France, 2001	800
DACH*, 2000	1000
Hungary, 2005	1000
Ireland, 1999	700
Italy, 1996	700
Netherlands, 2000	1000
Nordic countries, 2004	900
Poland, 2008	900
Portugal, 1998	600
Spain, 2007	1000
UK, 1991	700

* Recommendations for Germany, Austria and Switzerland

Recommended intakes for men vary between 600 and 1000 µg RE/day (Table 2). In some countries women have lower recommended intakes than men, but women need higher intakes during pregnancy (an extra 100 µg RE daily) and during lactation (up to an extra 700 µg RE daily). Preformed vitamin A is readily absorbed in the upper part of the small intestine. Absorption of provitamin-A carotenoids from natural sources varies widely and depends on numerous factors, such as dietary fat and fibre. Absorption of carotenoids in fortified foods and supplements is better than from fruits and vegetables.

Groups at the greatest risk of a poor vitamin A status are infants, young children and elderly. Vitamin A stores in infants are small, and depend on the mother's intake during pregnancy and lactation (if the baby is breastfed). Women of childbearing age are discouraged from eating liver and are therefore also at risk of deficiency. Febrile infections during childhood can rapidly deplete vitamin A stores by increasing requirements as well as losses. Low intakes are common in elderly people who do not eat a balanced diet. Vitamin A status can also be impaired as a result of intestinal and liver disorders.

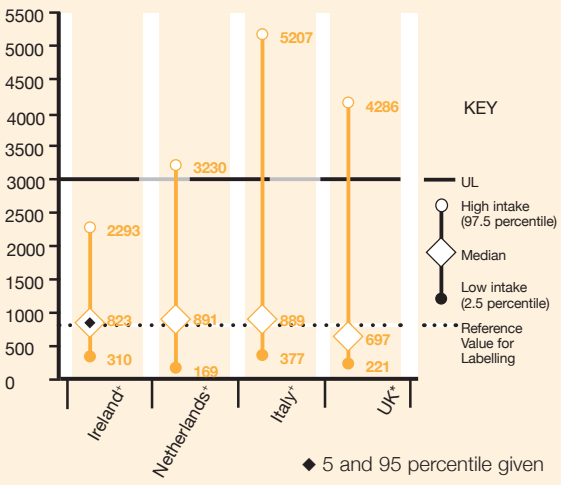
Intake

Surveys undertaken in Austria,[9] Ireland,[6] the Netherlands[10] and the UK[6] suggest that intake patterns vary considerably across Europe. In Austria, male intakes were between 105 and 125% of the RDA for all age groups. Female intakes ranged between 125% and 160% of the RDA (women aged above 56 years). In the Netherlands, male average intake exceeded Dutch recommendations for 1000 µg RE/day in adults, while for women average intake was 5% below the EU recommended 800 µg/day. Average intake was shown to be lower in Ireland and the UK.

In the UK, 50% of men and 49% of women did not meet UK national recommendations for vitamin A. Likewise in Ireland, daily average intakes for men (598 µg RE/day) and women (529 µg RE/day) were considerably below national recommendations. However, at the higher end of intake (97.5th percentile), intake in the UK and Germany appeared to be considerably higher than in other countries. In men, the highest (97.5th percentile) daily consumption of vitamin A was 4286 µg RE/day in the UK and 4480 µg RE/day in Germany compared to 3200 µg RE/day in Netherlands and 2887 µg RE/day in Ireland (Figure 1).[6,7,11] This is generally ascribed to the high liver intake in these countries which provides between 21 and 26% of total vitamin A intake.[6,7]

Comparative data available suggest considerable decreases in vitamin A intake over the last decade. Average vitamin A intake in the Netherlands dropped by 22% in men and 27% in women between 1987 and 1997.[10] Similarly in the UK, average vitamin A intake decreased by 39% in men and 46% in women between 1987 and 2001.[7]

Figure 1: Average daily intake (µg) of vitamin A for adult men (intake from all sources including food supplements* or excluding food supplements+)[6, 7, 10, 12]



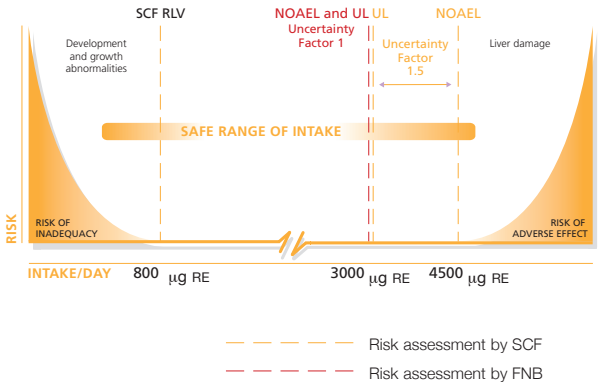
Safety

Reports of acute hypervitaminosis A over the past 60 years are mainly anecdotal, and usually concern ingestion of large amounts of shark or polar-bear liver. Symptoms experienced included headaches, bone and joint pain, nausea and dry skin. A bulging fontanelle is frequently reported in infants under 6 months of age treated for vitamin A deficiency with single large doses of vitamin A. It is always rapidly reversible, and is not associated with any permanent adverse effects. The severest problem associated with hypervitaminosis A is teratogenicity (malformations in the newborn).

Cases of liver toxicity in adults have been linked to the intake of high doses of retinol over long periods. The cause is thought to be an overloading of the liver's vitamin A storage capacity. The symptoms are usually reversible after the intake is stopped. Reports suggest that excessive retinol intakes may increase bone resorption and decrease bone formation[13] as well as increase blood fat and cholesterol concentrations.[14]

The EC Scientific Committee on Food has set the Tolerable Upper Intake Level (UL) for preformed vitamin A from diet and supplements at 3000 µg RE/day for adults with appropriately lower levels for children. Given that a large number of studies demonstrated a NOAEL of 3000 µg RE/day, there was considered no need to apply an uncertainty factor.[15] The Food and Nutrition Board also established a UL for vitamin A of 3000 µg RE/day. This UL was derived from a NOAEL of 4500 µg RE/day and an uncertainty factor of 1.5 (Figure 2). Women of childbearing age who are likely to become pregnant should not eat liver.[2]

Figure 2: SCF and FNB risk assessment



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VITAMIN B

The vitamin B complex comprises eight essential water-soluble micronutrients: thiamine (B_1), riboflavin (B_2), niacin (earlier known as B_3/B_4), pantothenic acid (earlier known as B_5), pyridoxine (B_6), biotin (earlier known as B_8 and vitamin H), folate (earlier known as B_9) and cobalamin (B_{12}).

Importance for health

The B vitamins act as coenzymes (helpers) in numerous biochemical reactions in the body. They are therefore essential for the proper growth, maintenance and functioning of all cells, tissues and organs. They are needed for the production and release of energy, hormones, neurotransmitters, blood cells and antibodies.

Some B vitamins are important for the optimal functioning of others: B_2, for example, is needed for the conversion of B_6 and folate into their active forms, B_2 and B_6 for the synthesis of niacin from the amino acid tryptophan. B_{12} and folate are jointly involved in homocysteine lowering. B_{12} is important for two key steps in fatty acid and amino acid metabolism.

B vitamins are part of many enzymes involved in energy production using carbohydrates, fatty acids and amino acids as a fuel for the body's endogenous energy source (ATP). Inadequate levels of B vitamins may, for example, lead to loss of appetite, fatigue, irritability, lack of concentration, dry skin, tingling sensations, muscle cramps and anaemia.

Heart health

High blood levels of homocysteine increase the risk for cardiovascular disease. Adequate levels of the vitamins B_2, B_6, B_{12} and folic acid are needed to remove homocysteine efficiently from the body. Studies have shown that supplementation with these vitamins can lower homocysteine levels significantly.[1,2]

Reducing cancer risk

B vitamins are important for protein synthesis. Niacin, for example, influences the tumor suppressor protein p53,[3] and has been shown to lower the incidence of cancer of the mouth and esophagus.[4,5] Another study linked high blood levels of B_{12} in women with a lower incidence of breast cancer.[6]

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of the B vitamins as a basis for health claims:

Vitamin B_1 (thiamine)[7,8]

- Normal energy-yielding metabolism
- Normal cardiac function
- Normal function of the nervous system
- Normal psychological functions

Vitamin B_2 (riboflavin)[9]

- Normal energy-yielding metabolism
- Normal metabolism of iron
- Maintenance of normal skin and mucous membranes
- Maintenance of normal vision
- Maintenance of normal red blood cells
- Protection of DNA, proteins and lipids from oxidative damage
- Reduction of tiredness and fatigue
- Maintenance of the normal function of the nervous system

Vitamin B_6[10,11]

- Normal protein and glycogen metabolism
- Normal function of the nervous system
- Normal red blood cell formation
- Normal function of the immune system

The B vitamins are essential for the proper growth, maintenance and functioning of all cells, tissues and organs.

- Regulation of hormonal activity
- Normal homocysteine metabolism
- Normal energy-yielding metabolism
- Normal psychological functions
- Reduction of tiredness and fatigue
- Normal cysteine synthesis

Vitamin B_{12} [12,13]

- Normal red blood cell formation
- Normal cell division
- Normal energy-yielding metabolism
- Normal function of the immune system
- Normal neurological and psychological functions
- Normal homocysteine metabolism
- Reduction of tiredness and fatigue

Biotin[14,15]

- Normal energy-yielding metabolism
- Normal macronutrient metabolism
- Maintenance of normal skin and mucous membranes
- Maintenance of normal hair
- Normal function of the nervous system
- Normal psychological functions
- Normal macronutrient metabolism

Niacin[16,17]

- Normal energy-yielding metabolism
- Normal function of the nervous system
- Maintenance of normal skin and mucous membranes
- Reduction of tiredness and fatigue
- Normal psychological functions

Pantothenic acid[18,19]

- Normal energy-yielding metabolism
- Normal mental performance
- Normal synthesis and metabolism of steroid hormones, vitamin D and some neurotransmitters
- Reduction of tiredness and fatigue

VITAMIN B

Food sources

B vitamins are found in most foods, but only in small amounts. An exception is vitamin B_{12}, which is only found in foods of animal origin (e.g. meat, eggs, milk) (Table 1). Most B vitamins are relatively unstable when exposed to heat, light and oxygen (exceptions are niacin and biotin) Considerable losses can occur during processing, storage and cooking.

Food supplements

B vitamins are generally formulated as a combination (B-complex) or included in multivitamin supplements. Single supplements of vitamin B_6 and nicotinamide are also common.

Table 1: Food sources of B vitamins [22,23]

Food	Serving	% of average daily dietary requirements provided by one serving					
		B_1	B_2	N*	PA**	B_6	B_{12}
Milk	100 ml	4	12	1	8	2	>20
Eggs	1 (50 g)	3	15	<1	15	5	30
Potatoes	100 g	10	1.5	10	10	15	0
Bread, wholewheat	1 slice (30 g)	10	4	7	3	3	<1
Legumes (beans, peas, lentils)	100 g	18	7	7-10	4-10	7-14	0
Pork, ham	100 g	35-75	18	30	18	30	35
Beef	100 g	8-12	12	25	8	25	>95
Beef liver	100 g	>100	>100	>100	>100	70	>100
Orange juice, fresh	100 ml	1	2	2	4	3	0
Breakfast cereals (fortified)	100 g	80	80	100	100	80	80

*Niacin, **Pantothenic Acid

A Gallup survey[20] of 6 European countries in 1999 showed that 23% of the population use food supplements. Of these users, 12% claim to take a vitamin B-complex supplement. On average, food supplements provide 1.7%-3.7% of total niacin intake, 3.6%-7.7% of total B_6 intake, 2.7%-6.4% of folate intake and 3.2%-6.1% of pantothenic acid intake.[21]

Findings from Germany suggest that food supplements significantly enhance the likelihood of meeting dietary requirements for B vitamins, but that for certain B vitamins, even regular food supplement users do not meet these requirements. In Germany, 48% of food supplement users do not meet national recommendations for biotin compared to 66% of non-users. One traditional concern about food supplements is that they may 'replace' the diet and reduce consumer intake of micronutrients from foods. Bietz et al. compared the dietary intake from food sources of regular users and non-users of food supplements. Although intake from food sources alone is sometimes greater in users of food supplements (as is the case for B_2, B_6, B_{12}) and sometimes less (B_1, B_{12} and niacin), the difference in intake from food sources is marginal (<2% in all cases except B_{12} which is 5% lower in food supplement users than non-users).[24]

Intake of B vitamins remains relatively low, even for regular users of food supplements. According to the latest intake survey in Germany even regular supplement users do not always reach the recommended daily intakes, specifically for B_1, B_2 and B_{12}.

Table 2 provides a review of the range of B vitamin content in food supplements sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Table 2: Range of B vitamins in food supplements on free sale (via health stores and supermarkets) in the major EU markets [25]

Country	B_1 (mg/day)	B_2 (mg/day)	B_{12} (µg/day)	Biotin (µg/day)	Niacin (mg/day)	PA (mg/day)	B_6 (mg/day)
Low dose							
Across EU	1.1	1.4	1.4	50	15	5	2
High dose							
Denmark	250	100	9	2500	100	90	200
Finland	75	75	500	600	35	35	75
Germany	12.2	16	10	5000	54	23	10
Ireland	100	200	25	500	450	500	50
Netherlands	50	200	3000	2500	500	550	200
Portugal	100	100	1000	1000	100	140	250
UK	100	100	2000	2000	250	140	100

Food fortification

A range of B vitamins are currently added to foods in Europe at levels which vary depending on national legislation. Specifically breakfast cereals, biscuits, dairy products and beverages often contain added B vitamins. In certain groups of the population breakfast cereals make an important contribution to the intake of a number of B vitamins e.g. around 15% of total vitamin B_1 and around 20% of vitamin B_2 intake in teenagers in the UK and Ireland. Some breakfast cereals also provide vitamins B_6 and B_{12} along with niacin.[26] In the UK the restoration of flour and bread with vitamin B_1 provides 15% of the total daily intake for some older adults. In Germany enriched beverages have made an important contribution to the B vitamin intake of adolescents. In accordance with EU legislation B group vitamins are required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

VITAMIN B

Recommended intakes

Recommended intakes for adults are shown in Table 3. Daily requirements of vitamin B_1 are affected by energy intake and those of vitamin B_6 by protein intake. The B vitamins have a high turnover rate in the body and most are not stored in any appreciable amounts, making regular intake essential. An exception is vitamin B_{12}, which is efficiently re-absorbed from the intestines and stored mainly in the liver. This explains why a B_{12} deficiency can take years to develop even in vegans.

Table 3: Recommended dietary allowances (RDA) of B vitamins for men[27]

Country	B_1(mg)	B_2(mg)	N(mg)	PA(mg)	B_6(mg)	Biotin(µg)	B_{12}(µg)
Belgium, 2009	1.5	1.5	16	5-12	2.0	30-70	1.4
France, 2001	1.3	1.6	14	5	1.8	50	2.4
DACH*, 2000	1.3	1.5	17	6	1.5	30-60	3
Hungary, 2005	1.1	1.6	18	-	1.3	-	2
Ireland, 1999	1.1	1.6	18	-	1.5	-	1.4
Italy, 1996	1.2	1.6	18	-	1.5	-	1.5
Netherlands, 2000, 2003	1.1	1.5	17	5	1.5	-	2.8
Nordic Countries, 2004	1.5	1.7	20	-	1.6	-	2.0
Poland, 2008	1.3	1.3	16	-	1.3	30	2.4
Portugal, 1998	1.2	1.3	16	-	1.3	-	2.4
Spain, 2007	1.2	1.8	20	-	1.8	-	2.0
UK, 1991	1	1.3	17	3-7	1.4	10-200	1.5

* Recommendations for Germany, Austria and Switzerland N - Niacin, PA - Pantothenic Acid

Intake

Surveys in Austria,[28] Germany,[29] Ireland,[21] the Netherlands,[30] and the UK[26] provide an indication of intake of B vitamins. According to the latest intake survey in Germany even regular supplement users do not always reach the recommended daily intakes, specifically for B_1, B_2 and B_{12}. In the UK, the proportion of those not meeting UK national recommendations for B vitamins does not generally exceed 10%. More recent recommendations (France, DACH and SCF) have proposed a requirement of 50 µg/day for biotin, an intake that is not met by 74% of men and 90% of women in the UK, although recommendations for biotin remain vague. Likewise in Ireland, the mean intake for most B vitamins is generally higher than recommended intakes, although for biotin and pantothenic acid, a significant proportion of men and women would not meet the SCF recommendations for these vitamins. The average diet of Austrian children aged >10 years and of some age groups within the elderly provided only suboptimal levels of thiamine, riboflavin and vitamin B_6 for both genders.

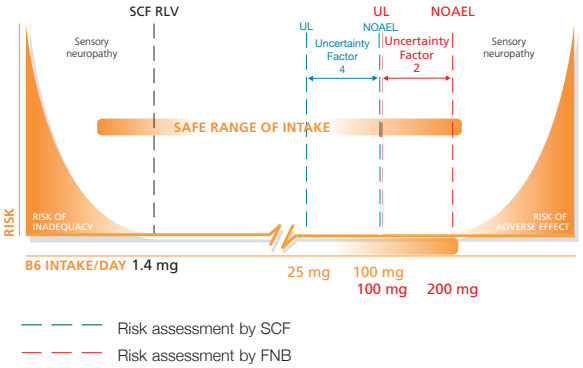
Comparative data illustrating trends in intake do not show consistent patterns for all B vitamins. Average intake of vitamin B_{12} in the Netherlands dropped by over 15% between 1987 and 1997. However, intake from vitamin B_6 increased in excess of 10%. Similarly in the UK, average intake of all B vitamins increased by up to 20% (B_1 intake in women) between 1987 and 2001 with the exception of vitamin B_{12} which decreased by around 5% in both men and women.

Safety

After assessing the B vitamins, the European Scientific Committee on Food (SCF) concluded that there is not enough data to establish a Tolerable Upper Intake Level (UL) for B vitamins with the exception of B_6 and niacin (see folate information sheet for findings on folate). No risk is associated with high intake of other B vitamins. Both the SCF and the Food and Nutrition Board of the Institute of Medicine were therefore unable to set ULs, as no adverse effect level could be identified.[31, 32, 33, 34, 35] The SCF set a NOAEL (No Observed Adverse Effect Level) of 100mg/day for vitamin B_6 taking into account the results of a study by Dalton and Dalton.[36] A UL of 25 mg/day was established by dividing the NOAEL by an uncertainty factor of 4 (to take into account the nature of intake data and uncertainties in the database). Combined intake from foods and food supplements is generally below this level. However, supplements available in some countries contain higher amounts. Neurotoxicity has been reported only after prolonged periods of treatment at extremely high doses (at least 500 mg daily for more than a year). Minor neurological symptoms have been recorded at lower doses (above 100 mg daily for more than a year). The symptoms were always reversible.[37]

The FNB in the USA set the adult UL for B_6 at 100 mg/day.[38] They excluded the report by Dalton and Dalton from their calculations, because they considered the study had methodological weaknesses. Niacin occurs in two forms, nicotinamide and nicotinic acid. High doses of free nicotinic acid (1-3 g/day for treatment of high blood cholesterol levels) are associated with flushing, gastrointestinal problems and abnormal liver function. Nicotinamide, the form of niacin generally used in vitamin supplements and for addition to foods, does not have such effects. The SCF has therefore set the adult UL for nicotinic acid at 10 mg/day, and the adult UL for nicotinamide at 900 mg/day. The UL for free nicotinic acid was derived from data on flushing following administration of a single oral dose. Flushing has not been reported for the bound forms of nicotinic acid present in foods.[26] The FNB did not make distinct risk assessments for niacin and nicotinamide and set a UL of 35 mg/day to cover the use of niacin and nicotinic acid from supplements and fortified foods.[38]

Figure 2: SCF and FNB risk assessment of Vitamin B_6



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VITAMIN C

Vitamin C (ascorbic acid) is a water-soluble vitamin. While most animals are able to synthesize vitamin C in their body, humans do not have this ability; they must obtain it through the diet. It is essential to some key mechanisms in the body and therefore fulfils several important roles in human health.

Importance for health

The biochemical function of ascorbic acid is based on its redox systems and as part of the body's antioxidant defence system.[1]

Connective tissues

Deficiency in vitamin C can lead to scurvy of which bleeding gums are the first sign since collagen synthesis requires vitamin C. Preliminary data suggests that Vitamin C might also contribute to stabilize atherosclerotic plaques.[2]

Role in the synthesis of neurotransmitters and peptide hormones

Copper containing enzymes compulsorily depend on vitamin C. One enzyme is involved in the synthesis of signalling compounds in the nerves. Another plays a role in the formation of peptide hormones in the brain.

Absorption of iron from the diet

Vitamin C changes iron in the stomach to a more bioavailable form (ferric iron to ferrous iron). This is particularly important for absorption of iron from vegetable sources (and therefore of particular importance for vegetarians and vegans).[3]

Maintaining the effectiveness of an efficient immune response

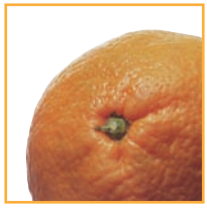
High doses of vitamin C reduce the synthetic capacity of histamine. Histamine concentrations are elevated in several complications of pregnancy like pre-eclampsia, abruption and prematurity.[4] Vitamin C has been shown to reduce the symptoms and duration of colds.[5]

Eye health

Together with other antioxidants vitamin C can delay the progression of advanced age-related macular degeneration (AMD) and vision loss.[6]

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of vitamin C as a basis for health claims:[7,8]

- Protection of DNA, proteins and lipids from oxidative damage
- Normal collagen formation and the normal function of bones, teeth, cartilage, gums, skin and blood vessels
- Increase of non-haem iron absorption
- Normal function of the nervous system.
- Normal function of the immune system.
- Normal energy-yielding metabolism
- Normal function of the immune system during and after intense physical exercise
- Reduction of tiredness and fatigue
- Normal psychological functions
- Regeneration of the reduced form of vitamin E



The biochemical function of vitamin C is based on its redox systems and as part of the body's antioxidant defence system.

Food sources

Vitamin C is widely distributed in fruits and vegetables and their juices (Table 1). Trace amounts are found in milk, grains and meat. Citrus fruits, blackcurrants, peppers, green vegetables, (e.g. Brussels sprouts and broccoli) and some tropical fruits (e.g. kiwi and guava) are particularly rich sources. Potatoes contain a lower level of vitamin C but make a significant contribution to many European diets due to the frequency and quantity of consumption. The body readily absorbs vitamin C whether from natural sources, fortified foods or food supplements.

Food supplements

A Gallup survey[10] of 6 European countries in 1999 showed that 23% of the population use food supplements. Of these users, 36% claim to take a vitamin C supplement once a week or more, the largest proportion of vitamin C supplement users being found in Poland. 39% of vitamin C users took dosages of less than 250 mg and 24% of the users took between 250 and 499 mg. The largest proportion of vitamin C supplement users taking 500-1000 mg can be found in France (15%): 6% of vitamin C users in total took products in this range, while 7% of users consumed over 1000 mg. On average, vitamin C supplements provide between 5.8% and 8.3% of total vitamin C intake.[11]

UK data indicate a highest average daily intake of vitamin C from supplements of 375 mg in women aged between 50 and 64 years (upper 2.5 percentile).[12] In Germany, the highest recorded daily intake from food supplements alone is in women of 180 mg (at 75th percentile).[13]

Table 2 provides a review of the range of vitamin C content in food supplements sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Table 1: Vitamin C content of raw and cooked foods[9]

Food	Raw (mg/100 g)	After boiling (mg/100 g)
Courgettes	21	11
Carrots	6	2
Cabbage, average	49	20
Cauliflower	43	27
Pepper, green	120	
Potatoes, new average	16	9
Potatoes, old, freshly dug	21	
Sweet potatoes	23	17
Tomatoes, raw	17	
Apples	6	
Bananas	11	
Blackcurrants (stewed)	200	115
Grapefruit juice	31	
Kiwi fruit	59	
Mango	37	
Oranges	54	

Table 2: Range of vitamin C in food supplements on free sale (via health stores and supermarkets) in the major EU markets[14]

Country	Vitamin C (mg/day)
Denmark	25 – 1000
France	25 – 500
Germany	25 – 1000
Italy	25 – 90
Netherlands	25 – 1500
Portugal	25 – 1000
Spain	25 – 60
Sweden	25 – 1000
UK	25 – 1500

VITAMIN C

Food fortification

Throughout Europe, fruit juice based and fruit flavour drinks are the foods most commonly enriched with vitamin C. A number of fruit containing breakfast cereals, fruit based desserts, jellies and dry dessert mixes also have vitamin C added or restored to replace processing losses. These products make a useful contribution to vitamin C intake especially for adolescents. Vitamin C is not frequently added to bread and pasta, as it is not very stable. In accordance with EU legislation vitamin C is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

Recommended intakes

Many EU Member States have established recommended dietary allowances (RDAs) for vitamin C, normally by population sub-group. The RDAs are normally for all ages from birth to old age, but the definition of the RDA differs by country. France and Germany, for example, take into account the need for optimal nutrition, whereas the UK looks at those levels required to prevent the symptom of deficiency i.e. scurvy. Hence, the actual numbers vary slightly. As more scientific data has become available on human requirements there is a discernible trend for the vitamin C RDAs in Member States to increase (Table 3). Pregnant and lactating women have higher needs.

Table 3: Recommended dietary allowances (RDA) of vitamin C (mg) in men in Europe[8]

Country	Men
Belgium, 2009	110
France, 2001	110
DACH*, 2000	100
Hungary, 2005	90
Ireland, 1999	60
Italy, 1996	60
Netherlands, 2000	70
Nordic countries, 2004	75
Poland, 2008	90
Portugal, 1998	45
Spain, 2007	60
UK, 1991	40

* Recommendations for Germany, Austria and Switzerland

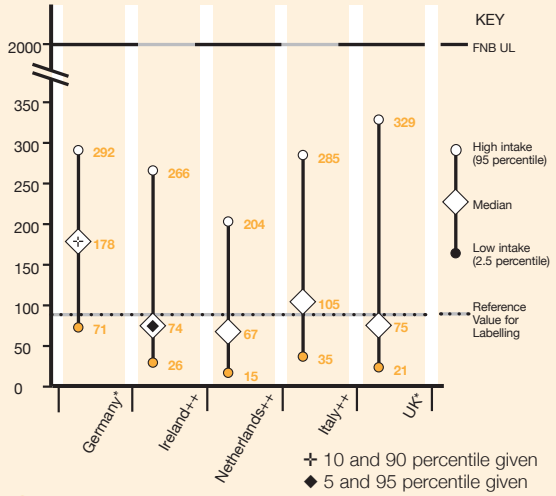
Intake

Surveys in Austria,[16] Ireland[11] and the Netherlands[17] suggest that close to 50% of the population meet national recommended dietary allowances for vitamin C. Intake of vitamin C is considerably higher in Germany and Italy (Figure 1). In the UK, the proportion of those not meeting UK national recommendations, namely 40 mg/day is approximately 20% of adults. More recent recommendations of 80 mg/day for vitamin C would not be met by 54% of adults.[12]

Comparative data illustrating trends in intake have generally shown an increase in vitamin C. In the Netherlands, average intake of vitamin C increased by 12% for the total population between 1987 and 1997[17] and in the UK, average intake of vitamin C increased by 36% in men between 1987 and 2001 and increased by 53% in women.[12]

In a survey of European consumers, vitamin C was most frequently taken to help protect against infections such as colds and flu especially in the winter months. The second most frequently cited reason was that the individual felt they didn't eat a balanced diet (e.g. not sufficient fruit and vegetables).[10]

Figure 1: Average daily intake of Vitamin C for adult men (mg - intake from all sources including food supplements* or excluding food supplements++).[10,11,12,17,18]



Stability

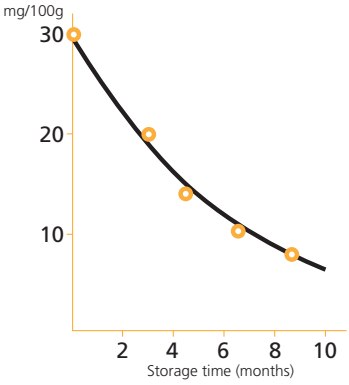
Vitamin C, or ascorbic acid, is an excellent antioxidant both in the body and in food and is nature's way of protecting fruits and vegetables from oxidative attack. When food is processed however, the structure of the food can be changed, for example in pressing an orange. This means that the tissues and cells are exposed to oxygen in the atmosphere and vitamin C is lost due to oxidation.

Stability continued

Vitamin C is lost from foods during cooking and storage. Potatoes for example will lose 15% of their vitamin C activity each month during storage at room temperature and a further 30-50% during boiling (Figure 2). Losses of vitamin C in milk are 25% on average after pasteurisation and 30% after UHT processing.

Processing, storage and cooking losses should be compensated where possible by restoration as part of good manufacturing practice. This cannot be done in unprocessed fruits and vegetables for technological reasons. Products such as soft drinks, milk and breakfast cereals are ideal products for restoration.

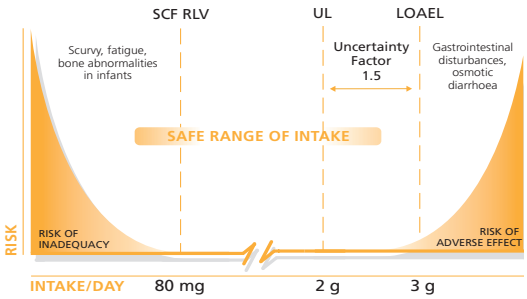
Figure 2: Effect of storage on vitamin C content of potatoes[19]



Safety

The Food and Nutrition Board made a detailed risk assessment of all major micronutrients and published the vitamin C work in 2000. Based on various studies it was concluded that an intake of 3 g/day may cause osmotic diarrhoea and this level was therefore taken as the LOAEL or Lowest Observed Adverse Effect Level. This figure was then divided by an Uncertainty Factor of 1.5 as the data was consistent to produce a Tolerable Upper Intake Level of 2 g/day (Figure 3).[20] More recently EFSA was not able to determine an UL for Vitamin C but concluded that the available human data suggest that supplemental daily doses of vitamin C up to about 1 g, in addition to normal dietary intakes, are not associated with adverse gastrointestinal effects, but that acute gastrointestinal effects may occur at higher intakes (3-4 g/day). The absorption of vitamin C is saturated at high doses, and therefore intakes above 1 g/day would be associated with negligible increased uptake and tissue levels, but an increased risk of adverse gastrointestinal effects.[21]

Figure 3: SCF and FNB risk assessment of vitamin C



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VITAMIN D

Vitamin D is a fat-soluble micronutrient that is only "conditionally essential", because it can be synthesized by UV-B light (290-319nm) from 7-dehydrocholesterol, a derivative of cholesterol, in the skin. The main form in the diet (and the form mainly produced in the skin) is vitamin D_3 (cholecalciferol). Vitamin D is metabolised in the liver to 25(OH)D, which is the major circulating metabolite of vitamin D and reflects vitamin D status. In the kidney 25(OH)D is converted to the active hormone calcitriol ($1,25(OH)_2D$). Vitamin D activity is measured in µg of cholecalciferol (1 µg = 40 IU). Foods of plant origin (mainly yeast and fungi) contain ergosterol, which can be converted in the plant to vitamin D_2 (ergocalciferol) by UV-B light.

Importance for health

Vitamin D plays a key role in promoting calcium absorption in the intestine and maintaining adequate serum calcium and phosphate concentrations to enable normal bone mineralization. In this way, it is important for the proper functioning of the skeleton. The classical manifestation of severe vitamin D deficiency is a softening of bones in children potentially leading to fractures and deformity (presenting as rickets in children and as a similar condition occurring as osteomalacia in adults). Vitamin D also plays an important role in the prevention of osteoporosis.

Furthermore, vitamin D demonstrates beneficial effects on muscle function and strength and thereby reduces the risk of falling.[1] Beside skeletal health (calcium homeostasis/bone health), emerging evidence suggests a non-skeletal benefit of vitamin D on multiple health outcomes.

Receptors for vitamin D exist in many tissues, indicating that it also has an important role in controlling cell growth and differentiation, as well as immune responses. There is accumulating data from epidemiologic studies that low vitamin D status is inversely associated with autoimmune disorders such as diabetes, rheumatoid arthritis and multiple sclerosis. Furthermore, various studies have shown an association between poor vitamin D intake/status and cardiovascular diseases and cancer of the breast, prostate and colon.[2] Some experimental studies indicate that vitamin D inhibits proliferation of colonic epithelial cells, and that lower levels may facilitate the growth of colorectal carcinoma.[3] A comprehensive review suggests that mean serum 25(OH)D levels of about 75 – 110 nmol/l provide optimal benefits for several health outcomes.[4]

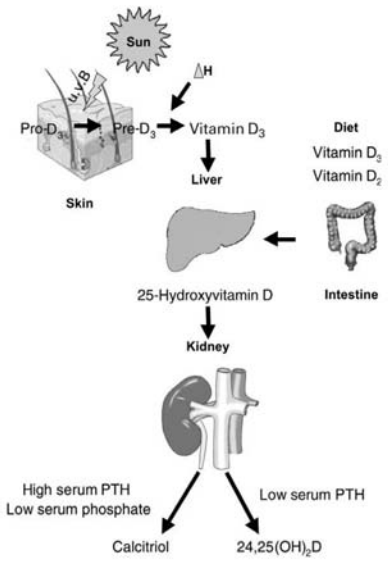
The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of vitamin D as a basis for health claims: [9,10]

- Maintenance of normal bone and teeth
- Normal absorption and utilisation of calcium and phosphorus and the maintenance of normal blood calcium concentrations
- Normal cell division
- Normal function of the immune system and healthy inflammatory response
- Maintenance of normal muscle function
- Vitamin D and calcium and maintenance of normal bone

Bone health

An adequate intake of vitamin D is needed to achieve a vitamin D status that is sufficient for normal bone and teeth mineralisation throughout childhood and adolescence and for bone maintenance in adults and the elderly.[5] Furthermore it is well established and confirmed in two meta-analyses that vitamin D can reduce the risk of osteoporotic fractures and falls in the elderly.[1,6] Based on randomized controlled trials (RCTs), there was a significant dose-response relationship between doses, 25(OH)D plasma level and the (reduced) number of falls and fractures. Available evidence of the highest dose tested to date in elderly subjects suggests that daily supplementation with at least 20-25 µg vitamin D (800-1000 IU) can help to reduce any non-vertebral fracture rates by 20%, hip fractures by 18%[6] and the risk of falls can be reduced by 19%.[1] This data is supported by epidemiologic observations showing a significant positive trend between higher serum 25(OH)D levels and hip bone density and lower extremity strength.[7,8]

Figure 1: The major metabolic pathways of vitamin D[11]



The classical manifestation of severe vitamin D deficiency is a softening of bones in children potentially leading to fractures and deformity.

Table 1: Food Sources of Vitamin D[12]

Food	Serving	% of average daily dietary requirements provided by one serving
Salmon	100 g	235
Herring	100 g	470
Sardines	100 g	120
Margarine (fortified)	15 g	5-20
Egg yolk	1	10

Food sources

Sunlight

Sunlight is the main source of vitamin D (Figure 1). Vitamin D_3 is formed from cholesterol when the skin is exposed to sunlight. During the summer months in Europe, about 15-30 minutes noonday sun exposure on legs and arms may be sufficient. However, sunburns should be avoided. As melanin absorbs UV-B, dark-skinned people produce less vitamin D from sunlight. Use of sunscreen (sun protection factor >8) reduces production of vitamin D by 95%. Vitamin D synthesis is also decreased in older age. In all of Europe (latitudes above 35) very little vitamin D is formed during the winter months.

Diet

Food sources of vitamin D are limited. Plant foods provide almost no vitamin D. The best sources are wild fatty fish and fish liver oils, and eggs from hens fed with vitamin D_3 (Table 1). Fish and fish products generally provide between 15 and 25% of vitamin D_3 intake and meat provides between 22 and 35% of overall intake. Eggs are another important source providing between 11 and 13% of total vitamin D intake.[13,14]

Food supplements

The oldest form of a vitamin D supplement is cod liver oil. Synthetic vitamin D_2, produced by irradiation of ergosterol, is still used in supplements, although it is now being increasingly replaced by vitamin D_3.

A survey of Irish dietary patterns found that supplements provide on average between 6.2% (men) and 11% (women) of total vitamin D intake.[11]

The range of vitamin D content in food supplements sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines) ranges from a daily dose of 2.5 to 35 µg. Food supplements sold in pharmacies and subject to specific controls are not included.

Food fortification

Fortification of margarine and fat spreads with vitamin D is common in the EU and even compulsory in a number of Member States. While EU legislation in principle allows the enrichment of foodstuffs with vitamin D since 2006[15] only a limited number of other foods are fortified – despite the fact that such foods might play an important role in improving the vitamin D status of certain population groups, for example older adults and strict vegetarians.

Dietetic foods

In accordance with EU legislation vitamin D is added in defined amounts to specific foodstuffs for particular nutritional uses, for example infant formulas and meal replacement products. Human milk provides only a marginal amount of total vitamin D activity, even when the mother has an adequate vitamin D status. Breast-fed infants are therefore commonly supplemented with vitamin D (400–500 IU/10–12.5 µg daily).

VITAMIN D

Recommended intakes

Recommended intakes for a number of EU countries are shown in Table 2.

Table 2: Recommended dietary allowances (RDA) of vitamin D (µg) for men in Europe[20]

Country	µg
Belgium, 2009	10-15
France, 2001	5
DACH*, 2000	5
Hungary, 2005	5
Ireland, 1999	0-10
Italy, 1996	0-10
Netherlands, 2000	2.5
Nordic countries, 2004	7.5
Poland, 2008	5
Portugal, 1998	5
Spain, 2007	5
UK, 1991	0

* Recommendations for Germany, Austria and Switzerland

Intake

With sufficient sunlight exposure no dietary vitamin D might be required. However, it becomes an important nutritional factor in the absence of sunlight and for the elderly. Factors affecting cutaneous vitamin D production, besides the surface of skin exposed to sunlight and the use of sunscreens, include geographic latitude, season, time of the day, weather conditions, level of air pollution, skin colour and age.

A substantial part of the European population does not get enough sunlight, especially during the winter months, to cover vitamin D requirements through endogenous production.

Surveys in Austria,[16] Ireland,[13] the Netherlands[17] and the UK[14] indicate that a substantial part of the European population has a vitamin D intake below the recommended dietary allowances (RDA). Table 2 provides recommended intakes for adults up to 65 years of age. Groups at the highest risk of a poor vitamin D status are infants and the elderly, as well as people with inadequate exposure of the skin to sunlight.

Serum 25(OH)D, a metabolite of vitamin D, is the best marker of vitamin D status and reflects dietary sources as well as cutaneous vitamin D production by UV-B light. Serum levels of 25(OH)D below 50-70 nmol/L are regarded as insufficient. Interestingly, more than 80% of Greek and Italian women, compared to 18% of Norwegian women were below this level. This may be due to a higher consumption of cod liver oil or vitamin D supplements as well as fortified products in Scandinavia.

Surveys from different European countries indicate that vitamin D deficiency is widespread, including pre-school children and the elderly (Table 3). Data from the SENECA study[18] in 824 elderly people from 11 European countries reveal that 36% of males and 47% of females had 25(OH)D levels below 30 nmol/L. A recent report indicates that hypovitaminosis D is prevalent and re-emerging as a major health problem globally.[19]

Table 3: Vitamin D status in different European population groups during summer and winter (adapted from Zittermann[11])

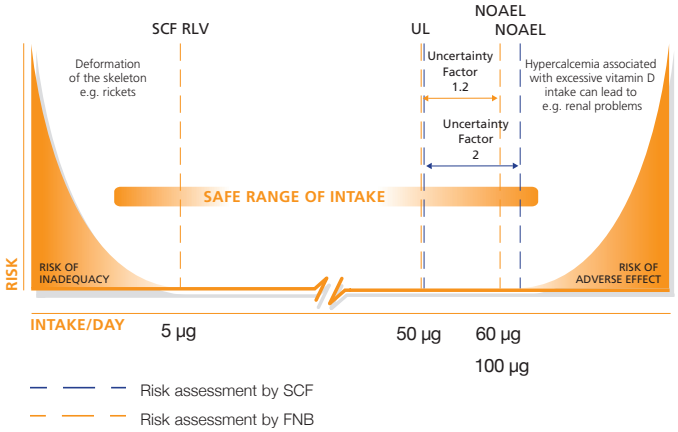
		Mean circulating 25 (OH)D level (nmol/L)	
Age group and country	Latitude (°North)	Summer	Winter
Children			
Germany	51	84	43
UK: white children	50-60	80	52
UK: dark-skinned children	50-60	-	36-42
Spain	43.5	75	32
Adolescents			
Finland	60	63	34
France	49	71	21
Young adults			
Finland	60	-	46
Germany	51	70	30
Elderly			
UK	50-60	35	23
Italy	42	-	28
Greece	35-38	-	24

Safety

The functional status indicator for vitamin D, for both safety and efficacy, is serum 25(OH)D concentrations. Efficacy for several health outcomes requires serum levels of 75 nmol/L or even higher while toxicity occurs at levels of 500 nmol/L or higher.[4,21]

Excessive intakes of vitamin D can lead to hypercalcemia (plasma calcium levels greater than 2.75 mmol/L or 11 mg/dL), and possibly to hypercalciuria (increased calcium excretion in urine)(Figure 2). Prolonged hypercalcemia can cause kidney stones, and calcification of soft tissues, including kidney, blood vessels, heart and lungs. Other symptoms of hypervitaminosis D include loss of appetite, loss of weight, weakness, fatigue, thirst, disorientation, vomiting and constipation. Toxicity is associated only with excessive supplemental intake (usually vitamin D dose greater than 20,000 IU/day (1250 µg daily).[16]

Figure 2: SCF and FNB risk assessment of vitamin D[22,23]



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VITAMIN E

Vitamin E is a generic term covering all tocopherols and tocotrienols which qualitatively exhibit the same biological activity as α–tocopherol. Therefore, vitamin E refers to α-, β-, γ- and δ-tocopherol, plus α-, β-, γ- and δ-tocotrienol.

Importance for health

Antioxidant and non-antioxidant roles

Vitamin E is long recognised as the body´s major lipid soluble antioxidant, and thus is fundamental in maintaining the integrity and functionality of the cellular membranes of all cells of the human body. As an antioxidant, vitamin E acts within cell membranes, protecting unsaturated fatty acids from oxidation. In doing so, the vitamin is oxidised itself and must be 'recycled' back to its active form, typically by vitamin C. Therefore, the two vitamins are closely interlinked and often investigated jointly.[1]

Due to its role as an antioxidant, a crucial role of vitamin E has been suggested for all conditions associated with increased oxidative stress, such as cardiovascular disease, diabetes, disorders involving chronic inflammation, preeclampsia, cancer, neurologic disorders, endurance exercise, increased exposure to oxidants, and others.

In addition to its antioxidant function, research demonstrated specific roles of vitamin E in signal transduction, gene expression, and regulation of other cellular functions.[2]

Immune function

Immune functions decline with age, which may relate to an increased vulnerability in elderly people to infections and other diseases. Numerous studies suggest a role for vitamin E in maintaining optimal immune status later in life.[3]

Heart health

Vitamin E has long been ascribed a role in preventing atherosclerosis and heart disease due to its beneficial effects on various mechanisms involved in atherosclerosis development (such as inhibition of LDL oxidation, anti-inflammatory effects, inhibition of smooth muscle cell proliferation). Nevertheless, the role of vitamin E in the prevention of heart disease is currently a matter of debate, as is the approach to oxidation and disease, where maintenance of oxidative balance may now be more appropriate.[4]

Biological activity

α-Tocopherol is the form of vitamin E that has the highest biological activity and is the most abundant in the human body. Nevertheless, other tocopherols such as γ-tocopherol may also have specific beneficial roles in human health.[5] The biological activity of the forms of vitamin E vary due to differences in their affinity to a liver protein - the so-called α-tocopherol-transfer-protein (α-TTP).[6]

To account for differences in biological activity of the various forms of vitamin E, the vitamin E content in foods, food supplements and fortified foods should be expressed in 'mg α-tocopherol equivalents' (mg α-TE).[7] Some products may, however, still carry the old unit for biological activity of vitamin E: 'International Units' (IU). 1.00 mg α-TE equals 1.49 I.U.

Food supplements and fortified foods may contain either natural source or of the synthetic form vitamin E. As natural source and synthetic vitamin E are not equivalent in chemical structure they differ in biological activity: the biological activity of synthetic vitamin E is lower than that of natural (source) vitamin E, in other words, more of the synthetic form is needed for the same effect.

Conversion factors for the various forms of vitamin E as used by the German, Austrian and Swiss Nutrition Societies and other bodies are given in Table 1.

Table 1: Vitamin E activity of various Tocopherols[8]

1 mg α-TE	1 mg RRR-α-tocopherol
	4 mg RRR-γ-tocopherol
	1.36 mg all-rac-α-tocopherol
	1.10 mg RRR-α-tocopheryl acetate
	1.49 mg all-rac-α-tocopheryl acetate
	1.21 mg RRR-α-tocopheryl succinate

Vitamin E is the body's major fat-soluble antioxidant and is needed to maintain the functionality of the cellular membranes of all the cells in the body.

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effect of vitamin E as a basis for health claims:[9]

- Protection of DNA, proteins and lipids from oxidative damage

Food sources

Vitamin E belongs to the group of fat-soluble vitamins. Vegetable oils, such as wheat germ oil or sunflower oil, are the best dietary sources, and nuts are another good source. The vitamin E content of fruit and vegetables, as well as of animal foods (meat, fish and dairy products) is relatively low (Table 2).

Table 2: Food sources of vitamin E[10]

Food	Fat (g)	Vitamin E (mg α -TE) /100 g food
Milk	3.6	0.1
Emmental cheese (45% fat/dry matter)	28.4	0.5
Butter	83.2	2.0
Olive oil	100.0	12.0
Soybean oil	100.0	17.0
Rape seed oil	100.0	23.0
Sunflower oil	100.0	63.0
Wheat germ oil	100.0	174.0
Cocoa butter	100.0	1.1
Salmon	13.6	2.2
Pork (meat only)	1.9	0.4
Wholemeal bread	0.9	0.8
Spinach	0.3	1.4
Tomato	0.2	0.8
Orange	0.2	0.3
Apple	0.6	0.5
Peanut	48.1	11.0
Hazelnut	61.6	26.0
Walnut	62.5	6.0

Food supplements

A Gallup survey of 6 European countries in 1999 showed that 23% of the population use food supplements (France 21%, Germany 27%, Italy 15%, Spain 16%, and UK 36%). Of these users, 19% claim to take a vitamin E supplement, vitamin E being most popular in Germany (21% of users). 42% of users took dosages of less than 100 mg, 17% between 100 mg and 400 mg and 18% took between 400 and 1000 mg. On average, food supplements provide between 5.5 and 11.9% of total vitamin E intake.[11]

In Germany, users of food supplements have, on average, an intake approximately 22% higher than non-users.[12] The UK data indicates a highest average daily intake of vitamin E from supplements of 270 mg in women aged between 50 and 64 years (97.5 percentile).

Table 3 provides a review of the range of vitamin E content in food supplements sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

VITAMIN E

Table 3: Range of vitamin E in food supplements on free sale (via health stores and supermarkets) in the major EU markets[13]

Country	Vitamin E (mg α-TE/ day)
Germany	10-540
Denmark	10-335
Finland	10-44.8
Ireland	10-270
Netherlands	10-350
Portugal	10-400
Sweden	10-825
UK	10-670

Food fortification

The most common types of foods currently fortified with vitamin E are soft drinks (such as multivitamin juices, 'ACE-juices', sports drinks), cereals and dairy spreads. Typical vitamin E concentrations in ACE-drinks are in the range of 1 – 2.5 mg/100 ml. The addition of vitamin E to oils and food rich in unsaturated fatty acids is in general not considered to be a fortification as such since the addition most often balances previous losses due to refining or production processes.

Recommended intakes

Several EU Member States, or governmental bodies, have established recommendations for intakes of vitamin E. Although these may vary between countries, there is general consensus that the vitamin E requirements depend on the intake of unsaturated fatty acids: increased intake of unsaturated fatty acids results in increased incorporation of such fatty acids into body cell membranes, thus increasing the need for antioxidant protection by vitamin E, the body's major lipid-soluble antioxidant.

Most recommendations for vitamin E intakes – or 'estimations for adequate intakes' – are largely based on the observation that vitamin E deficiency symptoms are usually not observed, so that the current intakes seem to meet the needs of the population (Table 4). With the further development of biomarkers for vitamin E status and requirements it will eventually become possible to establish science-based recommendations for vitamin E intakes to support optimal health.

Intake

Vitamin E status may be particularly low in people with impaired fat absorption e.g. those with celiac disease, cystic fibrosis, and pancreatic or liver disorders or those on prolonged low-fat diets, since the vitamin E content of foods is linked to the fat content. Genetic defects of lipid (hypo- and abetalipoproteinemia) or vitamin E metabolism (familial isolated vitamin E deficiency, FIVE), or conditions associated with increased oxidative stress, such as diabetes, or chronic inflammatory conditions may also have a negative impact on vitamin E status.

According to data from various surveys, mean vitamin E intakes in Europe are between 7 and 15 mg α-TE.[15] Using data reported for women in the Heidelberg cohort of the EPIC study as an example, the statistical distribution of vitamin E intakes was: 10th percentile 4.5 mg α-TE/day, 25th 6.7 mg α-TE/day, 50th 10.3 mg α-TE/day, 75th 15.7 mg α-TE/day, and 90th 22.4 mg α-TE/day. This means that more than 50% of the women had vitamin E intakes below the estimated adequate intake.[16] In Austria, inadequate intake of vitamin E (<80%) was the norm in women aged between 36 and 55 years. Similar intakes were also seen in Austrian men aged over 56 years.[17] In the UK, only 1-3% of the population did not meet national recommendations for vitamin E set in 1991 (3-4 mg/day), More recent recommendations of 12 mg/day would not be met by between 64 and 75% of the population.[18]

Table 4: Recommended dietary allowances of Vitamin E (mg α-TE) for men in Europe[14]

Country	Men
Belgium, 2009	15
France, 2001	12
DACH*, 2000	15
Hungary, 2005+	15
Ireland, 1999	–
Italy, 1996	–
Netherlands, 2000	11.8
Nordic countries, 2004	10
Poland, 2008	10
Portugal, 1998	10
Spain, 1998	12
UK, 1991	>4

*Recommendation for Germany, Austria and Switzerland.

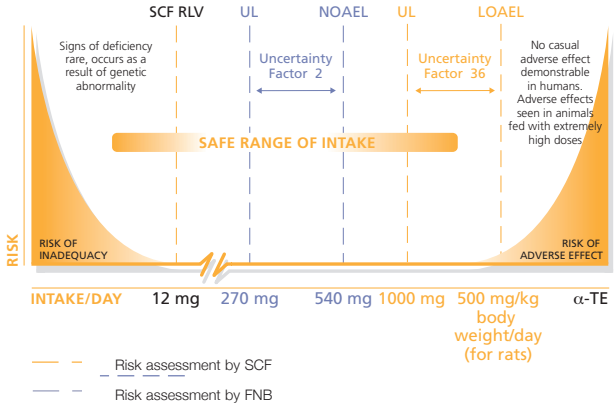
Safety

Unlike other fat-soluble vitamins such as vitamin A and vitamin D, vitamin E is generally safe even at higher intakes, and may be considered one of the safest vitamins, along with vitamin C. Three international expert groups have evaluated the safety of vitamin E: The EC Scientific Committee on Foods (SCF) 2003,[15] the UK Expert group on Vitamins and Minerals (EVM) – a scientific committee of the UK Food Standards Agency – 2003,[19] and the Antioxidant Panel of the Food and Nutrition Board (FNB), Institute of Medicine of the US National Academy of Sciences 2000.[20] Although all three expert groups draw on the same body of published data, the Tolerable Upper Intake Levels (UL) set by these groups differ considerably (Figure 1).

The SCF, in accordance with the other two groups, identified hemorrhagic effects as the critical adverse events, and used a placebo controlled dose response supplementation study in 88 healthy humans[21] to set the NOAEL (No Observed Adverse Effect Level) at 540 mg α-TE, the highest dose used in the study. Considering an uncertainty factor (UF) of 2 to cover for interindividual differences in sensitivity, the SCF established an UL of 270 mg α-TE for adults, which was rounded to 300 mg α-TE.[15]

The EVM established a NOAEL of 540 – 970 mg α-TE based on three placebo controlled human studies: Gillilan et al. 1977 (48 patients with stable angina pectoris, 1072 mg α-TE for 6 months);[22] Meydani et al. 1998 (s.a., 88 healthy subjects, 34, 134 or 537 mg α-TE for 4 months),[21] and Stephens et al. 1996 (CHAOS trial, 2002 atherosclerosis patients, 537 or 268 mg α-TE for a median of 510 (3-981) days).[22] A UF to account for interindividual differences was not considered necessary since the results of the larger trial by Stephens et al. support a NOAEL of 540 mg α-TE, so that the UL was established as 540 mg α-TE for supplemental vitamin E.[19]

Figure 1: SCF and FNB risk assessment for Vitamin E



The FNB considered data from several large human intervention trials as well as other clinical trials, but nevertheless concluded that there is insufficient human data pertaining to dose-response relationships – a key element in scientific safety assessment. Therefore, the panel used animal data to establish the LOAEL (Lowest Observed Adverse Effect Level), considered several aspects to be combined into the UF (severity of effects, pharmacokinetics in humans and animals, duration of studies and others, including an UF of 2 to extrapolate from the LOAEL to the NOAEL) and, in this way, set a Tolerable Upper Intake Level (UL) for adults at 1000 mg/day of any form of supplemental α-tocopherol.[20]

The extrapolation of considerably different ULs from the same databases is problematic for risk managers who need to take measures on the basis of this work, i.e, who may wish to set limits for the use of vitamin E in food supplements and fortified foods. It would therefore be desirable for different risk assessment bodies to consolidate their work to arrive at a single harmonized UL.

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FOLATE

Folate is a generic term for food folates (polyglutamate derivates) and folic acid. An additional intake of 400 µg per day of folic acid has been demonstrated to dramatically reduce the prevalence of neural tube defects (NTD), which are one of the most significant congenital causes of morbidity and mortality in infants, effecting in excess of 250,000 newborns every year worldwide.[1]

Importance for health

Neural tube defects

An additional intake of 400 µg per day of folic acid has been demonstrated to dramatically reduce the prevalence of NTD effect.[1] In Europe, more than 90% of women of childbearing age have intakes below this optimal level.[2] One strategy is to increase supplementation among the target population, although this depends on ensuring that the women receive folic acid prior to pregnancy, given that the neural tube often closes before women know they are pregnant. Public understanding of this problem in Europe is generally still poor, although campaigns have noted some success. The US authorities have implemented a policy to fortify flour with folic acid. Findings have suggested a reduction in NTDs of between 20% and 50% since fortification began.[3]

Heart health and homocysteine

The level of homocysteine is normally rigorously controlled within a narrow range in both human cells and circulating plasma. Even moderate elevation of homocysteine has been shown in numerous studies to be a risk factor for heart attacks and strokes.[4] A meta-analysis concluded that after adjustment for known cardiovascular risk factors a 25% reduction in plasma homocysteine is associated with a reduction in risk for ischemic heart disease of 11% and of stroke of 19%.[5] There has consequently been a lot of interest in determining how to decrease homocysteine plasma levels.

The level of homocysteine is controlled by the activity of three enzymes, each of which requires one or more vitamins for their activity.[6] These are cystathionine synthase (vitamin B_6), methionine synthase (vitamin B_{12}) together with methylenetetrahydrofolate reductase (MTHFR, folate and vitamin B_2). In all populations a common genetic variant (also called genetic polymorphism) exists of MTHFR. The consequence of polymorphism is a reduced activity of the enzyme in about 10% of the population and a significant but less dramatic reduction in about half of the population.[7]

As mentioned earlier, MTHFR uses riboflavin (vitamin B_2) as a cofactor. The reduced activity of the genetic variant CÆT 677 is due to loss of this cofactor. In a very important study, it has been shown that the reduced acitivity of this enzyme and consequently the resultant elevation of homocysteine is absolutely dependent upon the riboflavin status.[8] Further, in a human intervention study riboflavin normalised the activity of this enzyme in those with the common genetic defect giving them optimal homocysteine levels.[9]

Without an extensive laboratory investigation, most people don't know which of the nutrients they need and it seems prudent to take supplements containing folic acid together with the vitamins B_2, B_6 and B_{12} to be sure of having optimum homocysteine levels.

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of folate as a basis for health claims Lower case on folate:[10,11]

- Normal blood formation
- Normal homocysteine metabolism
- Normal function of the immune system
- Normal cell division
- Normal maternal tissue growth during pregnancy
- Normal psychological functions
- Reduction of tiredness and fatigue
- Normal amino acids synthesis

Folate plays an important role in several physiological functions including normal cell division, especially for cell systems with a high cell division rate (e.g. blood cells, mucosa of the gut).

Food sources

The consumption of folate must be regular, as human beings are unable to synthesise folate. Green vegetables provide one of the most important sources of folate. Spinach, salad, asparagus, tomatoes, cucumbers, whole-grain products, liver and some tropical fruits are also rich in folate. Only trace amounts are found in meat and fish (Table 1).

Table 1: Folate content in food[12]

Food	Dietary folate equivalent (µg/100 g)
Spinach	56
White cabbage	36
Broccoli	25
Salad	23
Tomatoes	20
Wholemeal flour	38
Orange	31
Orange juice	16
Avocado	30
Banana	16
Cheese	19-42
Milk	4
Egg	27
Chicken	5
Beef	3
Liver	242
Salmon	5

Food supplements

Despite the recommendations of relatively high folate intake, consumption of food supplements containing folic acid remains low. In Ireland, food supplements provide on average 2.4% of total folate intake for men and 6.4% for women.[13] However, in the Netherlands, where only 1.7% of the study population took folic acid supplements,[14] supplements provided approximately 50% of mean total folate intake.[9] The German Nutrition Survey of 2008 provides data on nutrient intake as consumed from usual diet and additionally from vitamin and mineral supplements. This study has demonstrated that over 80% of men and women do not reach the reference value of 400 µg/day dietary folate equivalent solely through the diet. The German recommendations for folate intake can only be reached if the normal diet is supplemented.[15] The greatest recorded intake from food supplements is among UK women aged over 50 years with the highest intake of total folate (97.5 percentile) who consumed a daily average intake of 90 µg.[16]

Table 2 provides a review of the range of folic acid content in food supplements sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Food fortification

Fortification of foods has not been generally allowed in many EU Member States until lately (e.g. Scandinavia, France, Greece), or limited to certain dietetic foods (Austria).[18] Special product categories such as breakfast cereals may be fortified with folic acid. In the UK, many cereals and breads are fortified with folic acid, providing 25-100 µg per serving. There is a range of food and beverages fortified with folic acid on the German market.[19] A primary prevention strategy of fortifying flour with folic acid as undertaken in the US, Canada, Australia and South Africa has not been implemented in the EU.[20]

Table 2: Range of folic acid in food supplements freely sold in EU markets[17]

Country	Content (µg/day)
Denmark	100-400
Germany	100-900
Ireland	100-400
Netherlands	100-1000
Portugal	100-400
Sweden	100-400
UK	100-800

FOLATE

Recommended intakes

The Recommended Dietary Allowances (RDA) is a general term to describe the intake levels estimated to be sufficient to cover the needs of the majority of the healthy population. The variation in recommended intake levels is due to the fact that each country has its own approach, correction factors and publications on which the recommendations are based. The recommended intakes vary between 200-400 µg/day (Table 3). Specific recommendations are often set for women of childbearing age. For example, in Austria, Belgium, Germany, Netherlands and the UK, it is recommended that women take a supplement of 400 µg/day from at least 4 weeks prior to conception until at least 8-12 weeks of pregnancy.

Table 3: Recommended dietary allowances for folate in Europe[21]

Country	Sub-group	RDA (µg/day)
Belgium, 2009	men	200
France, 2001	men	330
DACH*, 2000	men	400
Hungary, 2005	men	0.2
Ireland, 1999	men	300
Italy, 1996	men	200
Netherlands, 2003	men	300
Poland, 2008	men	400
Portugal, 1998	men	400
Spain, 2007	men	400
UK, 1991	men	200

* Recommendations for Germany, Austria and Switzerland

Intake

In most European countries, average folate intake does not meet national recommendations. The mean dietary folate intake of adults is 291 µg/day for men and 247 µg/day for women (Table 4). The highest folate intake was reported in the Parisian area of France, whilst the lowest folate intakes were found in Swedish and Dutch populations. These differences in folate intake partly reflect traditional dietary habits across Europe. A Mediterranean diet consisting of higher portions of vegetables, fruits and whole grains may help explain higher intakes of folate in France, Spain and Portugal.[22]

In spite of specific national recommendations (Table 3) for this population group, women of childbearing age in particular do not consume enough folate. In Europe, more than 90% of women of childbearing age are estimated to an increase in average daily folate intake has been seen (of 47 µg for men and 73 µg for women) between 1987 and 2001, but not sufficiently to meet recommendations of 400 µg/day.

Table 4: Mean adult* folate intake in EU countries (µg/day)[2, 7, 23]

	Mean intake of folate (µg/day)	
Country	Male	Female
Germany	236	211
Netherlands	215	173
Spain	317	303
Portugal	300	265
UK	311	213
Denmark	304	249
Sweden	230	194
Ireland	332	260

*Generally data for persons aged between 16 and 64, although this varies slightly from country to country.

Consumer understanding of folate

Only 1 in 3 European consumers know of the relationship between increased folic acid intake and reduced risk of neural tube defects.[14] Following an extensive campaign to improve public understanding of this relationship by UK authorities, awareness of the importance of folic acid in the UK among the target group increased from 9% in 1995 to 49% in 1999.[24] The impact of this initiative is also clear in a survey of the general population undertaken in 1999: when asked which vitamin is most associated with the prevention of birth defects, 24 % of UK respondents answered correctly, compared to 5% in Spain, 2% in Germany and 0% in France.[25]

Stability[26]

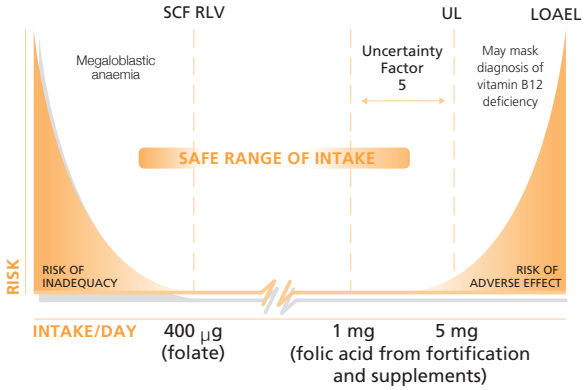
Naturally occuring food folate is rather unstable under exposure to oxygen, light and higher temperatures. Peas and spinach, for example, stored for 5 days, will lose around 50% of their folate content.[27] Substantial losses of folate also occur due to food processing or cooking.

Safety

The EC Scientific Committee on Food (SCF) and the US Food and Nutrition Board (FNB) made a detailed risk assessment of folate and their opinions largely converged (Figure 1). There is no adverse effect of folate from the diet. Excessive folic acid intake could mask vitamin B_{12} deficiency anaemia. Only 8 cases of adverse effects were reported at doses lower than 5 mg/day. A relatively large uncertainty factor of 5 was applied to this LOAEL (Lowest Observed Adverse Effect Level). The Tolerable Upper Intake Level was therefore established at 1 mg/day by the SCF to include dietary intake and intake from food supplements and fortified foods.[2] The FNB established a UL of 1 mg/day for intake of fortified foods and food supplements. It is unlikely that daily intake of folic acid from supplementation would regularly exceed 1 mg. Those at risk in relation to excessive intake of folic acid are those with a marginal intake of vitamin B_{12}, namely groups avoiding animal products, such as vegans.[28]

Recent evidence from animal studies, trend data for colorectal cancer incidence, and a randomised controlled trial have raised concerns of a possible association between high intakes of folic acid and promotion of cancer development and progression. An EFSA meeting held in 2009 addressed this potential problem and concluded that the current evidence does not show an association between high folic acid intakes and cancer risk but neither do they confidently exclude a risk. The uncertainties in relation to cancer risk highlight the importance of ensuring monitoring systems are set up for assessment of folic acid intake and status and NTD and cancer incidence in countries that decide to introduce mandatory fortification.[29]

Figure 1: SCF and FNB risk assessment of folic acid



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MINERALS

CALCIUM

Calcium is the major component of bones and teeth and is needed for many functions in the body. Calcium along with adequate Vitamin D intake is essential in the process of bone formation. For instance, inadequate calcium intake is linked to osteoporosis, a chronic and progressive bone disease that can affect the entire skeleton, leading to increased fracture risk.

Importance for health

Bone health

Osteoporosis is a chronic, progressive, bone disease that can affect the entire skeleton. It reduces bone mass and disrupts bone microarchitecture resulting in reduced bone strength and increased fracture risk. It is often characterized as a "silent" disease because it may go unnoticed as long as no symptoms appear. The disease is preventable, but because there are few warning signs until fractures occur relatively few people are aware of its presence during its early phase. It is an extremely prevalent disease in Europe. Around 1 in 8 European citizens over the age of 50 have spinal factures. One in 3 women and 1 in 9 men over the age of 80 will have a hip fracture.[1]

Calcium, together with adequate intake of vitamin D, is essential in the process of bone formation. The variation in bone mass can be ascribed to a wide range of factors, including genetics, smoking, excessive alcohol intake, physical activity, dietary habits and other life style factors accounting for 20% of that variation.[2] The importance of dietary factors should not be understated. It has been estimated that a 5% difference in peak-bone-mass will result in a 40% decrease in simple fractures.[2] Optimisation of peak bone mass through adequate calcium intake has been recognized as the most effective way to reduce risk of osteoporotic fractures later in life.[3] Trials have shown that supplementation with calcium may increase bone mineral accretion in children and adolescent girls.[4,5,6] The extent to which an intake above the level that allows the normal mineralisation of the bones can provide further benefits for the bones has been the subject of considerable discussion and the critical amount of calcium needed is not agreed upon. The most convincing results have been found when calcium supplementation has been given together with vitamin D probably due to the key role of vitamin D in calcium absorption.[7]

Mineralisation of teeth

The substance of the teeth is mainly composed of bone-like material consisting of a cellular, protein-containing matrix (hydroxyapatite) in which calcium salts are deposited.

Regulation of nerve excitability

The excitability of nerve and muscle cells is caused by changes in sodium and potassium conductance producing an action potential. A decrease in extracellular calcium increases the excitability by decreasing the amount of depolarisation necessary for the action potential, while an increase in extracellular calcium "stabilizes" the membrane by decreasing excitability. Change in calcium, availability is regulated via voltage-gated calcium channels.

Control of muscle contraction

Calcium is involved in the initiation of contraction of smooth muscle, as it is in skeletal muscle.

Blood coagulation

Activation of the blood coagulation system is dependent on the presence of calcium ions. Blood coagulation is initiated by intimal injury and causes expression of the so-called tissue thromboplastin factor. The key blood coagulation factor VII will, if complexed with tissue thromboplastin factor and in the presence of calcium, further activate the coagulation cascade.

Premenstrual syndrome

Studies have suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome and that calcium supplementation may be a simple, safe and effective approach.

Calcium and vitamin D

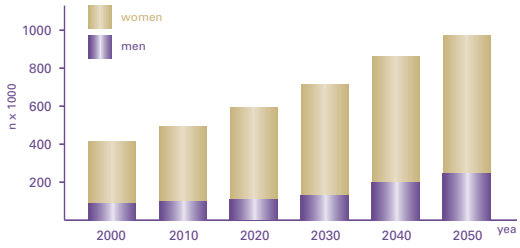
Primary calcium deficiency due to low calcium intake is a rather rare occurrence in most Western countries. Most often, hypocalcaemia is part of a hypovitaminosis D complex due to low exposure to sunshine and/or inadequate intake of vitamin D. Thus hypocalcaemia typically occurs together with hypovitaminosis D and is characterised by a serum calcidiol level below 10 ng/ml. Calcium and vitamin D supplementation decreases serum parathyroid hormone (PTH) and consequently bone resorption, particularly in individuals with a low dietary calcium intake and/or vitamin D insufficiency.

Calcium is the major component of bones and teeth and is needed for many functions in the body.

The social impact of osteoporosis

The European Commission has predicted dramatic increases in the future of the number of people likely to suffer hip fractures due to osteoporosis (Figure 1). As a result, it estimates that the percentage of hospital beds required for patients with spine or hip fractures will rise from 0.88% to 1.97% which would prove to be an enormous burden on hospital services throughout the European Community.[1]

Figure 1: 50 year forecast for hip fracture in the European Union[8]



The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of calcium as a basis for health claims:[8,9]

- Maintenance of normal bones and teeth
- Normal muscle function and neurotransmission
- Normal blood coagulation
- Normal energy-yielding metabolism
- Normal function of digestive enzymes
- Normal cell division and differentiation

Food sources

The most important dietary sources of calcium are milk and milk products, dried fruits and pulses (Table 1). Vegetables, bread, cereals, meat and fish may contribute significantly to he intake of calcium for people not consuming milk and dairy products, although additional calcium from supplements may be required.

Table 1: Food sources of calcium[10]

Food	Serving	Calcium (mg)
Milk	100 ml	130
Yoghurt	100 g	130
Cheddar cheese	50 g	360
Red beans	100 g, cooked	45
Chinese cabbage	100 g, cooked	590
Broccoli	100 g, cooked	70
Spinach	100 g, cooked	150
Rhubarb	100 g, cooked	200
White fish	100 g, cooked	10
Oily fish	100 g, cooked	20-60
Bread	100 g	10-70
Meat	100 g, cooked	10-15
Dried fruit	100 g	300

Table 2: Range of calcium content in food supplements on free sale (via health stores and supermarkets) in the EU[11]

Country	Calcium content (mg/day)
Austria	200 – 1000
Belgium	120 – 1600
Denmark	200 – 800
Finland	200 – 800
Germany	200 – 800
Netherlands	200 – 1500
Norway	200 – 1500
Sweden	150 – 800
UK	400 – 1200

CALCIUM

Food supplements

Food supplements containing calcium are often pure calcium products oriented at maintaining bone health (Table 2). Multivitamin and mineral products will also generally contain calcium. A survey of UK dietary patterns found that calcium supplements provide on average between 1% and 12% of total calcium intake. The greatest recorded daily intake of calcium from supplements was 324 mg/day in women in the UK aged 50-64 years with the highest level of intake (97.5 percentile).

Food fortification

Foods such as bread, baked products and breakfast cereals are fortified with calcium in Europe. In the UK, the legal requirement to add calcium to white and brown flour contributes around 10% to the calcium intakes of many adults. In a number of Member States fruit juice based drinks are frequently fortified, for example, in Germany and Austria where approximately 25% and 19% respectively of fruit juices on the market are fortified.[12] These beverages are a popular breakfast drink in these countries and make an important contribution to the daily nutrient intake of many adults and teenagers. For a number of consumers who do not eat or drink dairy products the enrichment of "non milk based" beverages with calcium is important to ensure adequate intakes. In accordance with EU legislation calcium is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

Recommended intakes

In general recommended intakes for calcium range between 600 and 1000 mg/day for adults (Table 3) and between 400 and 800 mg/day in young children. Sufficient dietary intake of calcium during childhood is associated with increased bone mass in adulthood and a reduced risk of fracture later in life. Calcium supplementation augments the rate of increase in bone mineral density and may also further reduce fracture risk.[13] Postmenopausal women and elderly men are at an increased risk of osteoporosis. Due to the low energy intake in the elderly, supplements of calcium and vitamin D are recommended.[14] Higher intake may also be beneficial for smokers as smoking is associated with bone loss and osteoporotic fracture. This may be due to decreased calcium absorption efficiency.[15]

Table 3: Recommended Dietary Allowances (RDA) of calcium (mg) for adults in Europe[16]

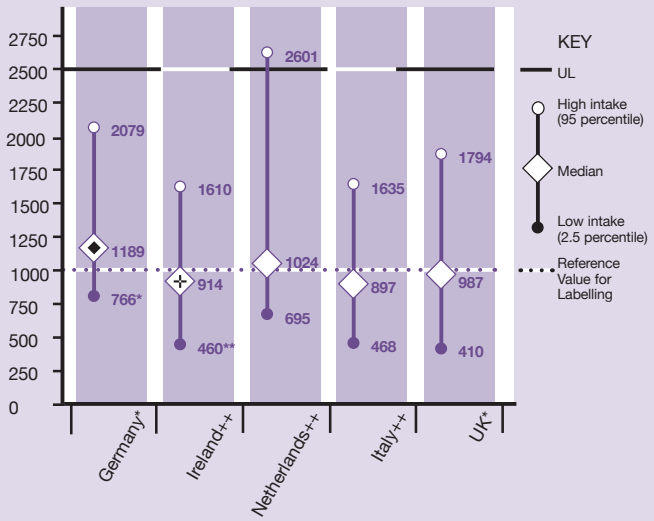
Country	Men (mg/day)
Belgium, 2009	900
DACH*, 2000	1000
France, 2001	900
Hungary, 2005	800
Ireland, 1999	800
Italy, 1996	1000
Netherlands, 2000	1000
Nordic countries, 2004	800
Poland, 2008	1000
Portugal, 1998	800
Spain, 2007	800
UK, 1991	700

* Recommendations for Germany, Austria and Switzerland

Intake

Austrian data demonstrates inadequate average intakes in all age groups among women and in all men except those aged 26-35 years.[17] A similar situation can be seen in the UK where 77% of women and 52% of men do not achieve recent recommendations of intake at 1000 mg/day,[18] and in Italy where 75% of Italian women and over 50% of men also fail to achieve this level of intake. In the Netherlands by contrast the majority of the population do meet daily recommendations (Figure 2).[18]

Figure 2: Average daily intake of calcium for adult men (mg) – (intake from all sources including food supplements* or excluding food supplements++).[18,19,20,21,22]

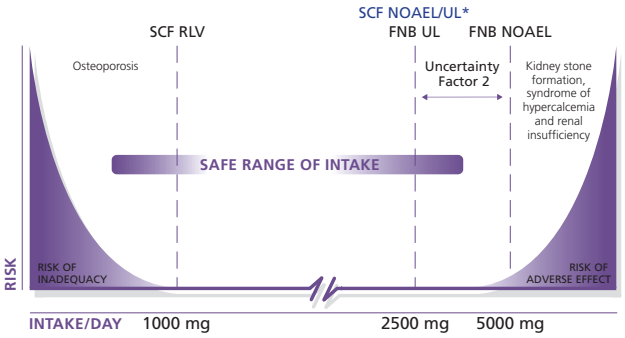


◆ 10 and 90 percentile given, ✢ 5 and 95 percentile given

Safety

Excessive intakes of calcium may lead to hypercalcaemia and renal insufficiency (Milk-Alkali Syndrome or MAS). The EC Scientific Committee established a No Observed Adverse Effect Level (NOAEL) of 2500 mg/day on the basis of a large number of long-term studies based on this level of intake. It considered that given the extent of the available database, no uncertainty factor needed to be applied and therefore established a Tolerable Upper Intake Level (UL) of 2500 mg/day for calcium from all sources of intake (Figure 3). The same level of 2500 mg/day has been established as a UL by the Food and Nutrition Board of the Institute of Medicine.[23] Guidance set by the UK Expert Group on Vitamins and Minerals recommends that there is no risk associated with daily supplemental dosages of 1500 mg/day.[24]

Figure 3: SCF and FNB risk assessment of calcium



* No uncertainty factor applied due to extensive database

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IRON

Iron is a key mineral for human metabolism. The healthy human body contains between 2.5 g (40 mg/kg: menstruating women) and 4.0 g (50 mg/kg: adult male) of iron. About 60% is found in the haemoglobin of the red blood cells, and 15% in myoglobin (in muscles) and various enzymes. Haemoglobin and myoglobin are proteins specialised in the transport and storage of oxygen. About 25% of body iron is stored (as ferritin or haemosiderin) mainly in the liver, spleen and bone marrow. Iron turnover is normally small. In the absence of bleeding (including menstruation) or pregnancy, about 1 mg iron is lost daily. During menstruation and lactation, iron loss may be twice as high. Iron requirements are also increased during pregnancy (5-6 mg daily in the second and third trimesters) to meet the needs of the foetus and the increased blood volume.[1]

Table 1: Prevalence of iron deficiency (as % of population) in European countries[2]

	Pregnant women		Adolescent girls	Children
	Depleted iron stores	Iron-deficiency anaemia	Depleted iron stores	Depleted iron stores
Denmark*	92%	18%	20%	2%
France	54–77%	9–30%	3–15%	14–38%
Italy	–	–	12%	7–25%
UK	25%	6%	21%	–

* Those not taking supplements. For those taking supplements the figures were 54% and 0% respectively.

Importance for health

Iron is required for a number of vital functions, including growth, reproduction, wound healing and immune function. The main role of iron is to carry oxygen to the tissues where it is needed. Iron is also essential for the proper functioning of numerous enzymes involved in DNA synthesis,[3] energy metabolism, and protection against microbes and free radicals.

Iron deficiency affects about 30% of the world population, and is one of the main deficiency disorders in Europe[4] (Table 1). People with iron deficiency may get short of breath and tire quickly; they have a lower resistance to infection, and may develop sores at the corner of the mouth, on the tongue and in the stomach. Severe iron deficiency results in anaemia associated with adverse pregnancy outcomes, and impaired mental and physical performance.

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of iron as a basis for health claims.[5,6]

- normal formation of red blood cells and haemoglobin
- normal oxygen transport in the body
- normal energy-yielding metabolism
- normal function of the immune system
- normal cognitive function
- normal cell division
- reduction of tiredness and fatigue

Food sources

Iron occurs in foods in two different forms: haem iron (mainly from haemoglobin and myoglobin in meat, poultry, and fish) and non-haem iron (from plants, dairy products and iron salts used to fortify foods). While haem iron accounts for only 10-15% of the iron in western diets, it may provide up to one third of total absorbed iron, because absorption is less influenced by other dietary factors than that of non-haem iron.

Absorption of non-haem iron is inhibited by phytates and polyphenols (in cereals, vegetables and legumes), tannins (in tea and coffee), calcium, and vegetable proteins (in soya and nuts), and is promoted by vitamin C (in fruit and vegetables), other organic acids and meat. It has been calculated that 1 g meat has the same enhancing effect on iron absorption as 1 mg ascorbic acid.[7]

Table 2: Food sources of iron[8]

Food	Serving	Iron content (mg)
Beef	100 g	3
Chicken, dark meat	100 g	1.5
Oysters	6 medium	5
Shrimp	8 large, cooked	1
Tuna, light	100 g	1.5
Raisin bran cereal	1 cup, dry	5
Raisins, seedless	50 g	1
Potato, with skin	1 medium baked	2.8
Kidney beans	100 g	3
Lentils	100 g	3.5
Tofu, firm	100 g	11
Cashew nuts	50 g	3

Iron is needed for body functions such as growth, reproduction, wound healing, and immune function.

Food supplements

Iron is sold in multivitamin and mineral supplements, in single iron supplements or in combination with vitamins and minerals such as vitamin D or magnesium. A German survey of nutritional supplement users showed that of the 36% of consumers using supplements, under 11% took iron supplements compared to 30% using magnesium supplements and 24% taking calcium supplements.[9]

A survey of Irish dietary patterns found that iron supplements provide on average between 2.7% (men) and 6.1% (women) of total iron intake.[10] The greatest recorded daily intake of iron from supplements was 11.4 mg/day in women in the UK aged 35-49 with the highest level of intake (upper 2.5 percentile).[11]

Table 3 provides a review of the range of iron content in products currently sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Table 3: Range of iron content in food supplements on free sale (via health stores and supermarkets) in the major EU markets[12]

Country	Iron content (mg/day)
Germany	2-100*
Denmark	2-66*
Ireland	2-15
Netherlands	2-20
Portugal	2-30
UK	2-15

* Food supplements in Germany and Denmark are generally sold at levels up to 20 mg/day, but individual products containing higher levels can be found on free sale.

Food fortification

In a number of Member States a range of foods are fortified with iron. Breakfast cereals in, for example, France, Ireland, Spain and the UK may be fortified with iron at between 15-25% RDA per serving. In the UK, Ireland and Germany such cereals provide around 5-20% of iron intake making a valuable contribution to iron intake, which is inadequate in certain groups of the population, including children and adolescents.[13,14] White wheat flour in the UK has iron added in order to restore one of the minerals lost during processing to its natural level. The iron added to flour, including that used to make bread is especially important in the diets of older adults. Iron is sometimes added to other cereal-based foods such as biscuits and also to fortified beverages at low levels. There are a number of technical and taste problems associated with adding iron to foods which means it cannot be added to all food categories. In accordance with EU legislation iron is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

IRON

Recommended intakes

Recommended intakes range between 8-15 mg daily for men (Table 4) and postmenopausal women, and 15-20 mg daily for menstruating women. Up to 30 mg daily is recommended for pregnant women (such amounts are difficult to achieve from food sources alone).

Requirements vary depending on the individual's iron status and the type of diet consumed. People with iron deficiency absorb a greater proportion of the iron consumed than those with adequate stores. Haem iron (found in meat, poultry and fish) is well absorbed; non-haem iron (found in other foods as well as in meats) is poorly absorbed, and its absorption is strongly influenced by inhibitors and enhancers in the meal. A diet of low iron bioavailability (high intakes of cereals, legumes and tubers, and negligible amounts of meat, poultry, fish and fruits/vegetables rich in vitamin C, as common in developing countries) containing 15 mg iron daily will contribute less than 1 mg to the body stores. A diet of high iron bioavailability (generous quantities of meat, poultry, fish and vegetables/fruits rich in vitamin C) can contribute up to 2-3 mg. Vegetarian diets have an intermediate iron bioavailability.[15]

Table 4: Recommended Dietary Allowances (RDA) of iron (mg) in Europe[16]

Country	Men
Belgium, 2009	9.1
France, 2001	9
DACH*, 2000	10
Ireland, 1999	10
Italy, 1996	10
Netherlands, 2000	9
Nordic countries, 2004	9
Poland, 2008	10
Portugal, 1998	9.1 – 13.7
Spain, 2007	10
UK, 1991	8.7

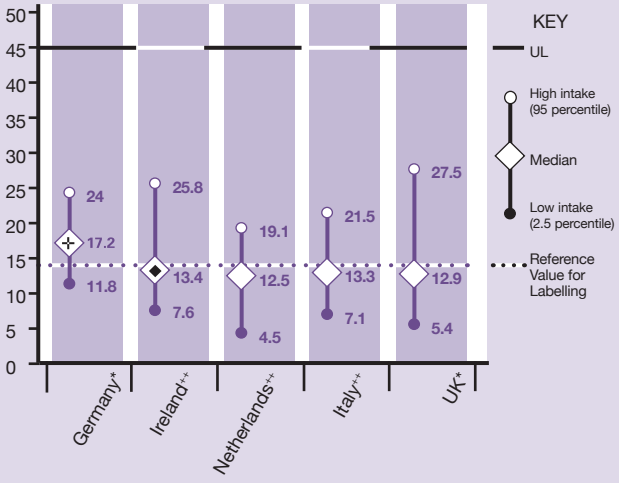
* Recommendations for Germany, Austria and Switzerland

Intake

Surveys in Austria,[18] Ireland,[10] the Netherlands[18] and the UK[11] suggest that inadequate intake of iron is widespread among women. In the UK, 84% of women (93% in the age group 25-34 years) do not achieve the recommended intake, while 50% consume less than 10 mg/day. Only 15% of men consume less than the recommended intake (Figure 1).

A similar pattern was found in the other countries. In the Netherlands, women aged 19-35 years consumed on average only 10.5 mg/day. In Austria, women's average intake of iron was 73% of the national recommendation, with women under 25 years most at risk of inadequate intake, and those over 56 years least at risk. Similarly, in Ireland, more than half of women surveyed did not meet the recommendations for intake with those aged 18-35 years recording the lowest intake.

Figure 1: Average daily intake (mg) of iron by adult men – (intake from all sources including food supplements* or excluding food supplements++)[10,11,17,18,19]



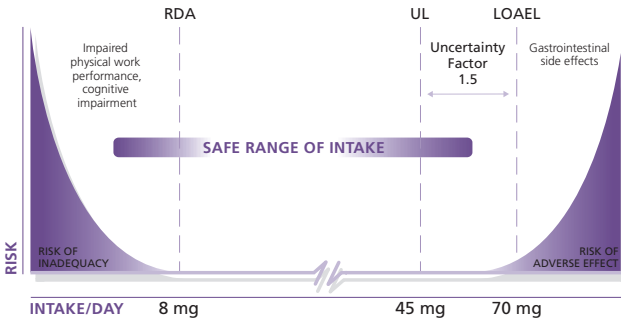
✛ 10 and 90 percentile given, ◆ 5 and 95 percentile given

Safety

High doses of supplemental iron have been associated with gastrointestinal side effects, especially when taken on an empty stomach. This risk was used by the Institute of Medicine's Food and Nutrition Board (FNB) to establish a Tolerable Upper Intake Level (UL) of 45 mg/day for iron (Figure 2).[20] Interference with zinc absorption is also possible when high doses are taken on an empty stomach (but not when taken with a meal). Iron overload may occur as a result of iron injections, blood transfusions or certain blood disorders, such as the hereditary disease known as haemochromatosis. This may be a risk factor for organ damage, cardiovascular disease and some cancers. The FNB therefore recommends that men and postmenopausal women avoid ironsupplements or foods highly fortified with iron.

EFSA has considered that the available data are insufficient to establish a tolerable upper intake level for iron.[21]

Figure 2: FNB risk assessment of iron



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MAGNESIUM

Magnesium is involved in about 300 enzymes and plays an important role in the body's metabolism, the regulation of blood pressure and bone cell function.

Importance for health

Magnesium is involved in about 300 enzymes and plays an important role in the body's metabolism, including muscle tension, the regulation of blood pressure and bone cell function.

Muscle cramps

Calcium and magnesium are essential for the contraction and relaxation of the muscle. If magnesium is not available in adequate amounts, it is probable that the muscle contracts constantly or earlier and relaxation does not occur. Research suggests that magnesium supplementation can lead to a lower frequency or even prevent muscle cramps.[1,2]

In addition, magnesium is thought to affect the tone of blood vessels and is able to change the tension that normally exists.2,3,4 A deficiency in magnesium may be a risk factor for preeclampsia, because magnesium can support vasodilation. For example Kisters et al. found, in a small-scale study, significantly lower plasma and intracellular magnesium concentrations in pregnant and preeclamptic women.3

Headaches

According to Altura and Altura, tense muscles in the neck or head might be a cause of headaches together with widened or cramped vessels or changed pressure in the head.[1] About 70% of persons with migraine or tension type headaches have cramped or weak muscles, and it was estimated that magnesium is influential in about half of these headache attacks.[1,4] Moreover, low magnesium concentrations in blood have been reported in migraine patients between attacks.[1,4] Peikert et al. have shown with 68 patients that 600 mg magnesium for a 12-week period could reduce the frequency of migraines in the last 4 weeks by 41.6% (placebo 15.8%). A significant decrease in drug consumption was also detected. The duration and intensity of the attacks decreased, but not significantly.[5]

Blood pressure

Epidemiological studies have shown that magnesium may be an important factor in maintaining normal blood pressure. When dietary magnesium intakes are low, a higher risk for hypertension has been detected.[2,6,7] Observational studies have often found an inverse relation between magnesium and hypertension, but intervention studies have not provided conclusive outcomes, suggesting that further investigation is needed. Van Leer et al. found a significant inverse association between dietary potassium, magnesium and blood pressure in 20,921 Dutch men and women, with the strongest association for magnesium.[7,8]

Bone health

About 50% of the body's magnesium can be found in bone, so magnesium is pivotal in mineral and bone homeostasis, bone cell function, growth and hydroxyapatite (a calcium phosphate mineral) crystal formation,[7] where it is understood to form a fixed and dynamic pool. This dynamic pool can be seen as a quick exchangeable magnesium store that is able to restore serum magnesium during deficiency. This pool declines during advancing age from 50% in early adolescence to 33% in adults to about 10% in the elderly of the magnesium concentrated in bone.[9,10]

According to Rude, in postmenopausal osteoporosis the serum magnesium content seems to be decreased. It is also supposed that women, especially those with diagnosed osteoporosis, can benefit from supplementation, although the evidence is not yet conclusive.[2,7]

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of magnesium as a basis for health claims:[11,12]

- Electrolyte balance
- Normal energy-yielding metabolism
- Normal muscle function including heart muscle
- Normal nerve function
- Normal cell division
- Maintenance of normal bone
- Maintenance of teeth
- Normal protein synthesis
- Reduction of tiredness and fatigue
- Normal psychological functions

Magnesium plays an important role in the body's metabolism, including muscle tension, the regulation of blood pressure and bone cell function.

Food sources

Magnesium can be found in varying concentrations in both animal and plant food sources. Green leafy vegetables (due to chlorophyll), unpolished grains and nuts are particularly rich in magnesium, contributing around 45% of dietary intake. Significant magnesium content can also be found in meat, milk, starches and eggs (Table 1). Lower concentrations can be found in refined or processed foods, as 80% of magnesium is lost during production.[7,13]

Table 1: Magnesium content in food[9,13]

Food	Serving	Magnesium content (mg)
Egg	1 egg	5
Milk	100 ml	13
Fats	20 g butter	0.3
	15 ml oil	0
Cereals	100 g bran flakes	178
	1 cup of cornflakes	11
Breads	1 slice of bread wholewheat, soft	24
	1 slice of bread, white, soft	6
Meat, fish	100 g cooked halibut	108
	100 g cooked flatfish	59
	100 g cooked lamb	23
Sweets	1 tbsp. honey	0.4
Juices	30 ml apple/tomato juice	3-15
Vegetables	1 baked potato with skin	54
	1 boiled potato, peeled before cooked	27
Fruits	1 raw unpeeled apple	6
	1 raw banana	34
Mineral water	1 litre	4-101

Food supplements

Of the 23% of regular supplement users, approximately 8% take supplements containing minerals. In a study of 6 European countries, mineral supplements proved to be most popular in Italy and Poland.[14] Magnesium intake from food supplements provides no more than 2.5% of total magnesium intake.[15] Magnesium intake from food supplements is highest in women aged over 35 years and men between 35 and 49 years.[16] Table 2 provides a review of the range of magnesium content in products currently sold freely in the EU, i.e. those that consumers can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Table 2: Range of magnesium content in food supplements on free sale (via health stores and supermarkets) in the major EU markets[17]

Country	Content (mg/day)
Germany	75-490
Denmark	75-600
Finland	75-350
Ireland	75-400
Netherlands	75-700
Portugal	75-400
Sweden	75-400

MAGNESIUM

Fortified foods

In Europe, approximately 3% - 9% of the mean total food energy may be derived from fortified foods. In relation to magnesium, there are technological and economical reasons, which limit the scope of magnesium fortification.[12] In Germany, where a wide range of fortified foods are sold only a limited number of products have added magnesium at moderate levels, for example, 15% RDA per 100g of product. Fruit juices and sport mineral drinks are the most popular products to be enriched with magnesium.[18] In France and the UK some breakfast cereals and cereal based products have added magnesium and in Spain and Italy magnesium fortified dairy products are available.[19] In accordance with EU legislation magnesium is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

Bioavailability

The bioavailability of magnesium is firstly related to the amount ingested: as intakes increase a lower proportion of the magnesium is absorbed. Secondly, the composition of the food can complicate the absorption of magnesium.[7,13] In a normal diet, about 30-50% of dietary magnesium is absorbed.[2,7]

Table 3: Recommended Dietary Allowances (RDA) of magnesium (mg) for men in Europe[11]

Country	Men
Belgium, 2009	420
DACH*, 2000	400
France, 2001	400
Netherlands, 2000 +	300-350
Nordic countries, 1996	350
Poland, 2008	400
Portugal, 1998	260
Spain, 2007	350-400
UK, 1991	350

* Recommendations for Germany, Austria and Switzerland

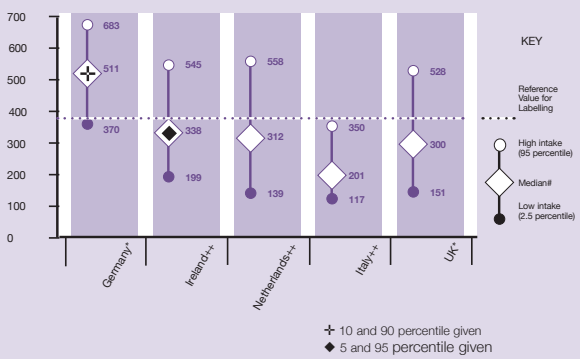
Recommended intakes

Recommended intakes for magnesium for a number of EU countries are shown in Table 3.

Intake

Surveys in Austria,[20] Ireland[15] and the UK[16] provide an indication of current intake of magnesium (Figure 1). Cereals and cereal products (including bread) provide 22-27% of magnesium intake and meat a further 13-16% of total magnesium intake. Alcoholic beverages, in particular beer, are another considerable source of magnesium contributing 10-12% to the diet. In Ireland, potato intake provides 15% of magnesium intake compared to 10% in the UK. In the UK, 50% of men and 72% of women did not meet the UK dietary recommendations for magnesium (300 and 270 mg/day respectively).[16] Intake in Ireland was shown to be marginally higher, although no population group on average met the figure of 375 mg/day set by the EU Scientific Committee for Food.[15] The highest intake was seen in the eldest age group (51-64 years) with a mean intake of 345 mg for men and 255 mg for women. Austrian data demonstrated that only women aged between 27 and 35 years and adult men less than 35 years were meeting national dietary recommendations.[20] Average daily intake appears to have decreased between 1987 and 2001 in the UK by 12 mg.[16]

Figure 1: Average daily intake of magnesium (mg) for adult men – (intake from all sources including food supplements* or excluding food supplements++)[15,16,21,22,23]



Specific reasons for taking magnesium

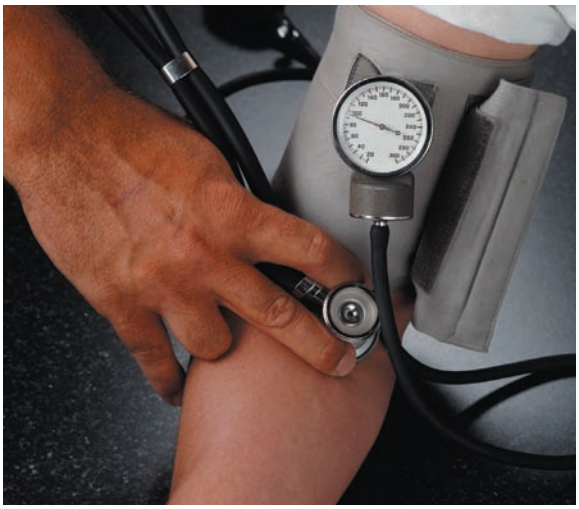
Certain population groups may be at a particular risk of not meeting recommended intakes for magnesium (Table 3). The elderly may be vulnerable due, for example, to lower appetite and problems with eating. Ageing is also associated with an increase in the urinary excretion and a decrease in absorption of magnesium. Diuretics, often used by the elderly, may also lead to higher excretion rates.[2,7]

Pregnant women may be at risk of deficiency due to reduced serum magnesium levels. An increase in lean tissue during pregnancy, minimised urinary magnesium excretion and elevated bone resorption during lactation, may lead to increased requirements during and after pregnancy.[7] Magnesium depletion sometimes develops during periods of high physical activity leading to muscle cramps. Recovery capacity may be reduced due to insufficient magnesium intake.[9]

Magnesium depletion is also very common in cases of chronic alcoholism. Lower intake, as alcohol replaces “normal” eating habits, and gastrointestinal disorders like diarrhoea, vomiting and gastritis deplete magnesium levels. Urinary losses are raised through the direct action of alcohol.[2,13]

Safety

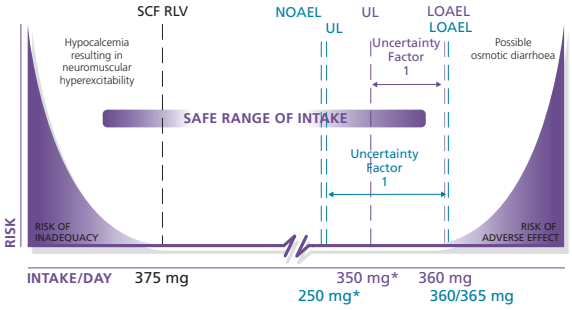
While no adverse effects are associated with dietary sources of magnesium, mild adverse effects such as diarrhoea can be associated with high amounts of supplementation.[7] The Scientific Committee on Food (SCF) and the Food and Nutrition Board (FNB) have estimated Tolerable Upper Intake Levels (UL) for supplementation with magnesium (Figure 2). The SCF LOAEL (Lowest Observed Adverse Effect Levels) was set at 360/365 mg/day, where a small number of adult subjects showed first signs of diarrhoea. At 250 mg weak laxative effects were not detected in adult men, women, lactating or pregnant women, so this was identified as NOAEL (No Observed Adverse Effect Level) by the SCF, without taking into account amounts from foods and beverages.



Subsequently the NOAEL was divided by an uncertainty factor of one, due to the mild and reversible nature of diarrhoea, to establish a UL for supplementation of 250 mg/day.[24]

The FNB estimated nearly the same LOAEL of 360 mg/day from non-food sources, although one study showed no effects at amounts up to 1200 mg/day. Like the SCF, this body estimated an uncertainty factor of about one resulting in a UL of 360 mg/day supplemental magnesium.[7]

Figure 2: SCF and FNB risk assessment of magnesium



— — — Risk assessment by SCF
— — — Risk assessment by FNB
*only supplementary magnesium

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SELENIUM

Selenium deficiency is linked to increased susceptibility to certain viruses like the Coxsackievirus B, an RNA virus. Coxsackievirus B causes Keshan disease, a disease of the heart muscle, characterised by the heart losing its ability to pump blood and, in some instances, disturbed heart rhythm, leading to irregular heartbeats, which only occurs in selenium deficient areas of China.

Importance for health

Selenium in the human body is present in two forms: selenomethionine and selenocysteine. Selenium substitutes for sulfur in the amino acids methionine and cysteine. Incorporation of selenocysteine into the so-called "selenoproteins" is specific and well controlled, and the selenoproteins have a defined functional role. Selenomethionine, on the other hand, is not specifically recognized as a selenium-compound, but is treated as "normal" methionine and as such is unspecifically incorporated into so-called "selenium-containing proteins" without a specific functional role. Upon degradation, selenium from selenomethionine may become available for selenocysteine biosynthesis (or be excreted).

Nearly 20 selenoproteins are known today. Those with an established function can be grouped as follows:

- Glutathione peroxidases - involved in antioxidant protection. One of the glutathione peroxidases also serves a non-antioxidant role as a structural element in human (and mammalian) sperm.
- Iodothyronine deiodinases - involved in the regulation of the active form of thyroid hormone.
- Thioredoxin reductases - regenerate vitamin C and are involved in the maintenance of cellular redox status.
- Selenoprotein P - suggested to be a blood transport protein for selenium and/or to be involved in antioxidant protection of blood vessel walls.

These selenoproteins differ in their sensitivity to an inadequate selenium status: glutathione peroxidase 1 is the first and most severely affected, followed by the other glutathione peroxidases. The activity of the other three selenoprotein classes is relatively well maintained in selenium deficiency. Today, the activity of glutathione peroxidase 3 is used to assess the adequacy of selenium status.

Immune system and infectious diseases

Infections are associated with increased oxidative stress due to the increased 'activity' of the immune system, therefore the importance of optimal antioxidant protection – involving glutathione peroxidases – is obvious. Further, studies have also demonstrated that certain viruses increase or even acquire their virulence in selenium deficient hosts. Keshan disease, a cardiomyopathy (a disease of the heart muscle, characterised by the heart losing its ability to pump blood and, in some instances, disturbed heart rhythm, leading to irregular heartbeats) which only occurs in selenium deficient areas of China, is caused by Coxsackievirus B. Coxsackievirus B, an RNA virus, has been shown to become virulent only in selenium-deficient hosts. Low selenium status and Coxsackievirus B infections have also been linked to myocardial infarction in patients in western countries.[1] Furthermore, selenium deficiency has been associated with increased virulence of influenza viruses.[2]

Such relations between selenium status of populations and/or individuals and infections are particularly intriguing considering that new influenza viruses as well as the first cross-over of HIV from non-human primates to humans originate from selenium deficient geographic regions.[3] It is therefore not surprising that selenium supplementation improved disease outcome and reduced mortality in patients with severe infections,[4] and improved various parameters of the immune status in healthy adults.[5,6,7]

Also, selenium status has been demonstrated to be a strong predictor of disease progression and mortality in HIV infections. For example, HIV patients with selenium plasma levels of 85µg/L or below – levels in northern European countries are often even lower – were 20 times more likely to die from HIV-related causes during the 3.5 year study period compared to patients with adequate selenium status.[8]



Selenium is an essential part of selenoproteins and may provide protection against viral infections.

Selenium and cancer

Epidemiologic evidence has also linked low selenium intakes to increased cancer risk. Two intervention trials support beneficial effects of selenium supplementation on certain types of cancer in subjects with low selenium status.[9,10] The association between selenium supplementation and prostate cancer is being investigated in a placebo-controlled intervention trial ("SELECT") in 32,000 men which is sponsored by the U.S. National Cancer Institute. In Europe, a placebo-controlled intervention trial ("PRECISE") is looking into the association between selenium supplementation and cancer in 42,000 subjects.

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of selenium as a basis for health claims:[11,12]

- Protection of DNA, proteins and lipids from oxidative damage
- Normal function of the immune system
- Normal thyroid function
- Normal spermatogenesis
- Maintenance of normal hair
- Maintenance of normal nails

Food sources

Selenium (Se) enters the food chain through plants, which take up selenium from the soil. Selenium in soil shows wide geographical variation, which greatly influences the selenium content of foods, and, consequently dietary selenium intake. For example, intakes in Finland have more than doubled from around 40μg to around 90μg due to the nationwide supplementation of fertilizers with selenium that began in 1984.[13] On the other hand, mean intakes of selenium in the UK have declined from 60 μg to around 34 μg/day mainly due to a change from high selenium wheat imported from the US to wheat grown in Europe, which is lower in selenium.[14]

In foods, selenium is generally present as a constituent of the amino acids methionine and cysteine, therefore selenium content is linked to protein content. Although the actual selenium content of foods is quite variable, as explained above, meat, fish and eggs are generally regarded as good sources of selenium, while dairy products and plant foods contribute less to the dietary selenium intake. According to data from Denmark and Germany, meat and meat products alone contribute 30 - 40% of the selenium intake, while meat, cereals, fish, eggs and milk together contribute approximately 80%.[15,16] Drinking water does not contribute to selenium intake.

SELENIUM

Food supplements

Selenium is sold as a single nutrient in supplements, but is more commonly found in combination with antioxidants or in a multivitamin and mineral supplement.

Table 1 provides a review of the range of selenium content in food supplements currently sold freely in the EU, i.e. those that the consumer can find on the shelves of supermarkets and health stores (including products that in some countries may be registered as medicines). Food supplements sold in pharmacies and subject to specific controls are not included.

Table 1: Range of selenium in food supplements on free sale (via health stores and supermarkets) in the major EU markets[17]

Country	Selenium (µg)
Germany	25-100
Denmark	25-125
Finland	25-50
Ireland	25-200
Netherlands	25-200
Portugal	25-200
Sweden	25-100
UK	25-300

Fortified foods

Selenium is not frequently added as a fortificant to generally consumed foods in Europe.

In accordance with EU legislation selenium is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

Recommended intakes

Recommended intakes for selenium for a number of EU countries are shown in Table 2.

Intake

Data on selenium intakes in various European countries is surprisingly scarce compared to what is available for other micronutrients. The UK Expert Group of Vitamins and Minerals (EVM) reports the mean UK intake to be 39 µg/day, and the 97.5th percentile to be 100 µg/day.[19] Mean selenium intakes presented by the EC Scientific Committee on Food (Table 3) are generally lower than those currently recommended in most Member States.

Table 2: Recommended Dietary Allowances (RDA) of selenium (µg) in Europe[18]

Country	Men
Belgium, 2009	70
France, 2001	60
DACH*, 2000	30-70
Hungary, 2005	75
Ireland, 1999	55
Italy, 1996	55
Netherlands, 2000	50-150
Nordic countries, 2004	50
Spain, 2007	70
UK, 1991	75

*Recommendation for Germany, Austria and Switzerland.

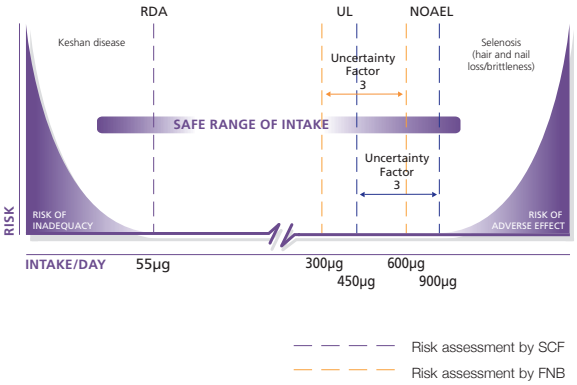
Table 3 : The mean selenium intakes of non-vegetarian adults in European countries[18]

Country	Selenium intakes (µg/day)
Belgium	28 - 61
Denmark	41 - 57
Finland	100 - 110
France	29 - 43
Netherlands	40 - 54
Norway	28 - 89
Sweden	24 - 35
UK	63

Safety

Excessive intake of selenium is associated with selenosis which may cause symptoms such as hair or nail loss, mottled teeth and skin lesions. These symptoms have been observed in a man taking 913 µg/day and no signs of selenosis were associated with intakes of 850 µg/day.[20] On the basis of these studies, the Food and Nutrition Board set a NOAEL (No Observed Adverse Effect Level) of 800 µg/day and SCF a NOAEL of 850 µg/day (Figure 1). To take into account potential uncertainties in the studies and variation between individuals particularly sensitive to selenium, the SCF and FNB selected an uncertainty factor of 2 and 3 respectively. On this basis, the SCF derived a Tolerable Upper Intake Level (UL) of 300 µg/day and the FNB a UL of 400 µg/day.

Figure 1: SCF and FNB risk assessment of selenium



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ZINC

Zinc plays an important role in body functions like the immune system, wound healing, stimulation of bone formation and normal functioning of the retina. For instance, wound healing involves new immune cell formation that removes bacteria from wounds and also results in the growth of new tissue.

Importance for health

Immune system

Zinc plays an important role in cellular processes, such as the humoral and cell-mediated immune defence. The normal activity of special immune cells and biological activity in a series of lymphokines can only be maintained when zinc is present in effective concentrations.[1,2] Some studies have demonstrated a relationship between zinc intake and reduction in the length and severity of a cold. For example, Prasad et al. showed that symptoms only lasted 4.5 days in a group of 48 persons taking about 24 mg zinc daily for a 12-day period compared to 8.1 days in the control group.[3]

Skin health

The process of wound healing consists of various stages of tissue reconstruction. During the inflammatory process, special immune cells remove bacteria from the wound and further cells are needed in the growth of new tissue. Zinc is thought to have a beneficial role in new cell formation.[4]

Bone health

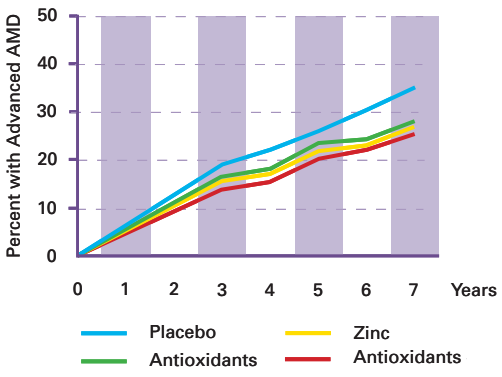
Zinc is contained in crystals forming bone matrix and is required to stimulate bone formation and inhibit bone decomposition. It is probable that zinc, in combination with calcium, has a positive influence on osteoporosis risk.[5] This is particularly the case for growing children due to zinc's importance in "peak-bone-mass". For elderly women, particularly those affected by osteoporosis, who have lower serum zinc levels and higher urinary excretion rates, this relationship is also particularly important.[1] For example, a Swedish study has shown that low phosphorus and zinc intakes in middle-aged and elderly men showed increased fracture risk.[6] Due to poorly balanced diets and worse absorption, the risk of deficiency increases in the elderly; in the USA 75% of people aged 60-90 years did not meet dietary zinc recommendations.[5] In Europe about 414,000 hip and 1,400,000 vertebral (spinal) fractures are estimated to occur each year.[7]

Eye health

760 per 100,000 people in Europe suffer from visual impairment.[7] The results of research into the role of zinc in age-related macular degeneration (AMD) and dark adaptation have been inconclusive. It is known for certain, however, that the retina contains a high concentration of zinc compared to other human tissues, which assists the normal functioning of the retina. Furthermore, it seems likely zinc plays a role in the phototransduction process, so that deficiency may result in night-blindness and poor dark adaptation. The apparent positive influence of zinc on AMD may be explained by the lower zinc concentration in the retinal pigment epithelium in persons affected by AMD.[8]

In the AREDS report, the relation between high dose intake of antioxidants or zinc (80 mg) or a combination of both on AMD and visual acuity was examined in 3640 persons for 6.3 years. The positive effect of visual acuity was only statistically significant in the group treated with zinc and antioxidants. After treatment a risk reduction for AMD of 17% compared to placebo was noted for antioxidants, and 21% for those taking zinc. The greatest risk reduction, about 25% was associated with subjects taking antioxidants and zinc (Figure 1). Therefore a combination of zinc and antioxidants might be an effective treatment in severe AMD.[9]

Figure 1: Risk of developing advanced AMD[10]





Zinc plays an important role in body functions like the immune system, wound healing, stimulation of bone formation and the normal functioning of the retina.

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of zinc as a basis for health claims:[11,12]

- Normal function of the immune system
- Normal DNA synthesis and cell division
- Protection of DNA, proteins and lipids from oxidative damage
- Maintenance of normal bone
- Normal cognitive function
- Normal fertility and reproduction
- Normal metabolism of fatty acids
- Normal acid-base metabolism
- Normal metabolism of vitamin A
- Maintenance of normal vision
- Maintenance of normal skin
- Normal protein synthesis
- Maintenance of normal serum testosterone concentrations
- Reduction of tiredness and fatigue
- Normal carbohydrate metabolism
- Maintenance of normal hair
- Maintenance of normal nails
- Normal macronutrient metabolism

Food sources

Although zinc is present in a wide variety of foods, there is a considerable difference in zinc content between meat and vegetables (Table 1). Red meat, beef, shellfish, whole wheat and unrefined cereals are an extremely good food source of zinc. During milling about 80% of protein in cereals and consequently zinc content is lost. Vegetables, fruits and milk are commonly low in zinc.[1,13,14]

Food supplements

Multivitamin and mineral supplements containing zinc at a range of 2-20 mg as well as single zinc supplements at a range of 15-50 mg are currently available on the EU market.[15] Zinc supplements provide on average around 2-4% of total zinc intake.[16] In Germany, where about 22% of women and 18% of men take supplements at least once a week, 8.8% of men and 12.5% of women take mineral supplements. Women aged 60-69 tend to be the greatest users of mineral supplements, whereas for men the intake is at its lowest in this age group.[17]

Fortified foods

In the US, fortification with zinc is a common practice, especially in breakfast cereals (usually at levels of around 25-100% of the RDA[1]), flour, bakery products and macaroni.[14] Fortification with zinc is not widespread in the EU, although some breakfast cereals are enriched and currently provide around 6% of daily zinc intake.[18] There are a number of organoleptic problems associated with the addition of zinc to foods, which requires careful selection of the mineral compound. In accordance with EU legislation zinc is also required to be added to specific foodstuffs for particular nutritional uses, for example, infant food, meal replacement products and dietary food for special medical purposes.

Table 1: Zinc content in food[1]

Food	Zinc content (mg/kg fresh weight)	Category
Oysters, wheat germ	>50	extremely high in zinc
Meat (beef, calf, pork, poultry), organs (liver, kidney, heart)	20-50	high in zinc
Egg, milk, cheese, fish, potatoes, whole-grain bread	5-20	moderate in zinc
Fruits, green vegetables, fats, white bread	<5	poor in zinc

ZINC

Bioavailability

The low absorption rate for zinc of about 15-40% is characteristic of all minerals. As intake increases, the rate of absorption decreases. Shellfish and wholemeal bread are particularly rich in zinc and, containing proteins to which zinc are easily bound, are especially conducive to absorption.[1] By contrast, vegetables contain both a smaller amount of zinc (with the exception of whole grain, nuts and leguminous plants) and higher levels of phytate which diminish absorption. For example, zinc absorption of phytate rich meals is about 15%.[19] Furthermore, some substances with low molecular weight such as amino acids, hydroxy acids and other organic acids stimulate absorption by increasing zinc solubility.[19,13]

Some interactions with other micronutrients are well known. For instance, high iron intakes seem to reduce zinc absorption by competing with zinc for uptake into the body. This is of particular concern during pregnancy and lactation when higher intakes of iron are encouraged. High-dose zinc intake is also thought to cause copper deficiency.[13,14]

Recommended intakes

In general recommended intakes for zinc range between 7 and 15 mg/day for adults (Table 2) and between 2 and 10 mg/day in young children. Certain population groups are particularly at risk of zinc deficiency.

Elderly

As elderly people often take diuretics and thereby increase zinc excretion and their zinc absorption is often reduced, a higher intake is required in this population group. In the US, inadequate zinc intake was noted for about 45% of people above 60 years. This was improved through use of supplements to almost a quarter.[14,20]

Table 2: Recommended Dietary Allowances (RDA) of zinc (mg) for men in Europe[21]

Country	Men
Belgium, 2009	11
France, 2001	12
DACH*, 2000	10
Hungary, 2005	10
Ireland, 1999	9.5
Italy, 1996	10
Netherlands, 2000	7
Nordic countries, 2004	9
Poland, 2008	11
Portugal, 1998	4.2-7
Spain, 2007	15
UK, 1991	9.5

* Recommendations for Germany, Austria and Switzerland

Vegetarians

Although zinc intake seems not to be different between vegetarians and people with mixed diets, vegetarians may have up to 50% higher dietary requirements due to impaired bioavailability.[15]

Children

As zinc appears to be crucial to cell division and protein synthesis, the impairment of physical growth is one of the most relevant clinical features.[2, 22] In that zinc deficiency seems to affect linear growth and weight gain, sufficient zinc intake in children is essential.[13]

Pregnancy/Lactation

During pregnancy, zinc in the plasma is about 15-35% lower than in non-pregnant women. Several studies have examined the influence of maternal zinc status and birth weight: 54% found that zinc supplementation had an effect on birth weight.[14]

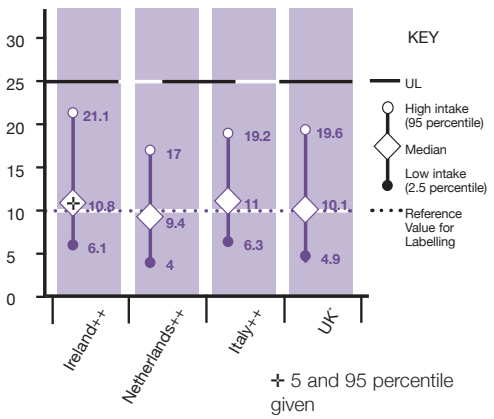
Sportsmen and women

In competitive and non-competitive sports and especially during rehabilitation, higher metabolic rates in micro and macronutrients are common. Sportsmen often also have elevated nutrient losses due to perspiration (higher for minerals than for vitamins), or lower dietary intake in order to achieve their weight class. In such cases elevated intakes are needed.[1, 23]

Intake

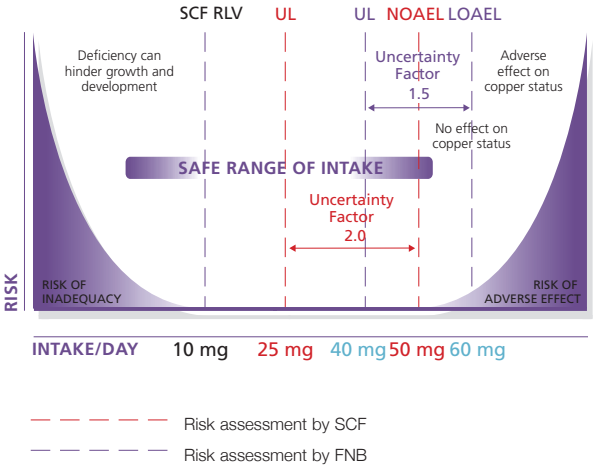
It is estimated that about 50% of the population in Europe do not have optimal nutrition in vitamins and minerals.[7] Recent surveys in Austria,[24] Ireland[16] and the UK[18] provide an indication of current intake of zinc (Figure 2). In the UK, 49% of men and 85% of women do not meet the recommended intake of 10 mg/day set by the SCF in 2003, although requirements for women are generally understood to be lower (Table 2).

Figure 2: Average daily intake (mg) of zinc for adult men (intake from all sources including food supplements* or excluding food supplements++)[16,18,25,26]



Safety

In excess, zinc intake can have adverse effects such as loss of appetite, diarrhoea, headaches, nausea and abdominal cramps. At intakes higher than 45 mg, immune system function can be negatively affected.[25] The Food and Nutrition Board (FNB) and the Scientific Committee on Food (SCF) have set different Tolerable Upper Intake Levels (UL) for zinc (Figure 2). Drawing on a study on supplemental intake of 50 mg/day, the FNB established a Lowest Observed Adverse Effect Level (LOAEL) of 60 mg.



The UL was calculated by dividing the LOAEL by an uncertainty factor (UF) of 1.5 to take into account the potential different sensitivities between individuals, and to extrapolate a No Observed Adverse Effect Level (NOAEL) from a LOAEL. A higher UF was not justified given the rarity of the relevant adverse effect, namely reduced copper status in humans.[13]

The SCF determined a NOAEL of 50 mg/day at which adverse effects on copper status were not apparent. Because of the small number of study participants involved in the study on which this NOAEL was based, an uncertainty factor of 2 was applied, resulting in a UL of 25 mg/day.[15]

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CAROTENOIDS

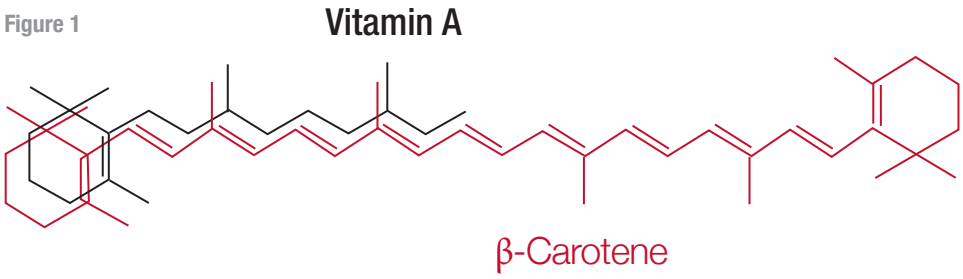
BETA CAROTENE

β-carotene is the most well known representative of the group of carotenoids, which are abundant in fruit and vegetables. Together with α-carotene, β-cryptoxanthin, lutein, zeaxanthin and lycopene it exerts two major functions: as a colour, it renders flowers attractive for insects, and as a bioactive substance it supports essential processes in the metabolism of micro-organisms, plants, animals and humans.

β-carotene is synthesized exclusively in plants; it is the predominant carotenoid in yellow to orange and green leafy vegetables and yellow fruits. A diet rich in fruit and vegetables as recommended by health authorities provides about 5 mg β-carotene per day.[1]

β-carotene can be cleaved to yield vitamin A. Thus, as pro-vitamin A, it is an important complementary source of vitamin A for humans who do not eat enough dairy products or liver. As a strong antioxidant it protects our cells from the damaging effects of free radicals and can improve the function of the immune system. As a result of these protective properties it is thought that an adequate intake of β-carotene is associated with reduced risk of chronic health problems like heart and eye diseases.

Figure 1



Importance for health

Conversion to vitamin A

The most important function of β-carotene is its conversion to vitamin A. Vitamin A is essential for normal growth and development, immune system function, skin and bone health, and vision. The rate of conversion is regulated by the body's vitamin A status, thus preventing an overdosing of vitamin A (hypervitaminosis A).[1] Theoretically, one molecule of β-carotene can be split into two molecules of retinol (Figure 1), but the conversion is by far less efficient. Therefore, official conversion factors assume that, in order to form 1 µg of retinol, 6 µg of β-carotene are required.[2]

Antioxidant

Like the other carotenoids, β-carotene is a powerful antioxidant that can interfere with free radicals. Oxygen is essential for life, but is also involved in oxidation processes that produce highly reactive singlet oxygen and other reactive species. These "free radicals", also called ROS (reactive oxygen species), are needed for certain physiological processes such as immunological defense, but under conditions of oxidative stress with an excess of these molecules, cell lipids, proteins or DNA may be damaged, thus impairing the normal function of these important biomolecules.[3] Therefore, oxidative stress has been suggested to play a role in the development of a number of degenerative diseases, such as cancer and cardiovascular disease, cognitive impairment and Alzheimer's disease, immune dysfunction, cataracts and macular degeneration, as well as in the ageing process itself.[4] A number of factors, such as air pollution, smoking, environmental toxins, UV light, and inadequate intake of dietary antioxidants can place us at risk of oxidative stress.

Observational and prospective epidemiological studies have shown inverse relationships between the risk of degenerative diseases linked to oxidative stress and carotenoid intake and/or blood levels.[5] It appears that β-carotene can contribute to health when taken at adequate levels, but may have adverse effects when taken in high doses by subjects who are long-term heavy smokers or who have been exposed to asbestos.[5]

β-carotene as a predominant carotenoid in yellow to orange and green leafy vegetables and yellow fruits, is an important antioxidant that protects body cells from the damaging effects of free radicals and can improve the function of the immune system.

Immune function

The immune system protects our body against infections, cancer cells and foreign substances. The function of the immune system can be compromised by many factors, such as stress, pollution and strenuous exercises. Many of the health problems traditionally associated with ageing are now also related to the immune system. Nutrition can have an important influence on immune function and it has been suggested that β-carotene can enhance immune cell function.[6] Early studies demonstrated the ability of β-carotene and other carotenoids to prevent infections.[7] Some clinical trials have found that β-carotene supplementation improves several biomarkers of immune function. The number of white blood cells and the activity of natural killer cells could be increased by β-carotene supplementation.[8,9,10,11]

These immune stimulating properties of β-carotene may be through its prior conversion to vitamin A that is known to be essential for normal immune system function.[7] Another explanation is the antioxidant actions of β-carotene that may protect cells in the immune system from damage by reducing the toxic effects of reactive oxygen species (ROS).[7] However, recent studies suggest that β-carotene may help boost the immune system in a more complex manner and much has yet to be done to truly understand the molecular mechanism of action.[7] Thus, it can be concluded that β-carotene stimulates and enhances several processes of the immune system.

Skin protection

Human skin is continuously exposed to internal and external influences that may alter its condition and functioning. As a consequence, the skin may undergo alterations leading to photo ageing, inflammation, immune dysfunction, imbalanced epidermal homeostasis, or other skin disorders.[12] Probably the most visible one – premature skin ageing, or photo ageing – results largely from continued exposure to ultraviolet (UV) radiation from the sun. Photo ageing is characterized clinically by wrinkles, mottled pigmentation, rough skin, and loss of skin tone; the major histological alterations are with the dermal connective tissue.[13]

β-carotene and other carotenoids can protect light-exposed tissues. They can be used as an oral sun protectant in combination with sunscreens for the prevention of sunburn and have been shown to be effective either alone or in combination with other carotenoids or antioxidant vitamins.[14] Although the sun-protection factor is relatively small compared with that of topical sunscreens an increased threshold for sun exposure before burning can be achieved and the severity of sunburn can be reduced.[15] When β-carotene was applied as such or in combination with vitamin E for 12 weeks, erythema formation induced with a solar light simulator was diminished from week 8 onwards.[16] Thus, at least 4 weeks of supplementation are recommended prior to sun exposure to ensure its accumulation in the skin.

β-carotene taken orally can be regarded as a nutrient that can protect and provide skin health from the inside. Adequate β-carotene levels in the body may contribute to a more long-term defence against UV light.[17,18]

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of vitamin A, which apply as well if β-carotene is used as a source of vitamin A.[19]

- Normal cell differentiation
- Normal function of the immune system
- Maintenance of normal skin and mucous membranes
- Maintenance of normal vision
- Normal metabolism of iron

BETA CAROTENE

Food sources

β-carotene rich plants show colours in the orange and yellow range but other phytonutrients may be more dominant. Therefore, besides vegetables such as carrots and pumpkins also green spinach, kale, and broccoli are rich sources of this nutrient (Table 1).

Table 1: Typical sources of β-Carotene (mg/100 g)[20]

Vegetables		Fruits	
Carrots:	1.8-14.7	Mango:	0.1-3.7
Kale:	2.8-14.6	Watermelon:	0.2
Broccoli:	0.5-1.1	Peaches:	0.1-0.4
Green Peppers:	0.1-0.3	Apricots:	0.6-6.4
Oranges:	0-0.5	Spinach:	3.0-6.7

Absorption and metabolism

The portion of ß-carotene that is absorbed, transported, and utilized (bioavailability) by our body is influenced by a number of factors. In general, β-carotene is not as available from fruit and vegetables when compared to β-carotene from dietary supplements. Four conditions are necessary for adequate absorption.[21]

- Digestion of the food matrix; availability may vary between 5% or lower (from raw vegetables such as carrots) and higher than 70% (food supplements containing β-carotene in emulsified form)
- Formation of lipid micelles in the gastrointestinal tract: the presence of fat in the intestine for the absorption of β-carotene is mandatory, although the amount of dietary fat required to ensure absorption seems low (approximately 3-5 g per meal)[22]
- Uptake of the carotenoid containing micelles into intestinal mucosal cells
- Packaging into specific lipoproteins (chylomicrons) for transport via the lymph to the blood circulation

Food processing, such as mechanical homogenization or heat treatment, has been shown to increase the bioavailability of carotenoids from vegetables.[23]

Intake

Average intakes of β-carotene from food sources are reported to be in the range of 2-5 mg/day (Table 2).[24]

Intake from food supplements and fortification

β-carotene is also listed as a generally permitted yellow food colour E 160a in the European Additives legislation. In Europe, the estimated average exposure to β-carotene from food additives is around 1-2 mg/person/day. β-carotene intakes from food colours use for German, French and British adults range from 0.4 to 1.9 mg/day (Table 3).[25]

Food supplements

According to the European Food Supplements Directive 2002/46/EC, β-carotene is permitted for use in dietary supplements as a source of vitamin A. In Great Britain the contribution of β-carotene from supplements to the total intake was negligible.[25] Intake data from Germany demonstrated that daily users of β-carotene-containing food supplements consume only 1.6 mg/d β-carotene from this source.[26]

Fortified food

The most important fortified foods are fruit-based drinks.[27] The presently used levels of β-carotene lie in most cases below 5 mg/litre for beverages and below 10mg/kg for solid food.[24]

Recommended intakes

In Europe, the recommended intake is based on the assumption of a conversion factor of 6, therefore 4.8 mg β-carotene is needed to meet the requirement of 800 µg vitamin A. From epidemiological studies it can be concluded that a plasma level of 0.4 µmol/L β-carotene should be aimed at in order to benefit from the preventive potential. This can be achieved with 2-4 mg/day.[28] Typical plasma concentrations of β-carotene in men in different European regions are listed in Table 4.

Table 2: Intake of β-carotene from food (mg/d); median (5-95 percentiles)

Country	Men	Women	Ref
Ireland: all sources	2.09 (0.41-5.81)	1.91 (0.48-5.41)	29
UKa): all sources	1.56 (0.30-5.03)	1.46 (0.26-4.68)	25
UKa): from food	1.56 (0.30-5.03)	1.42 (0.23-4.57)	25
Germanyb): Potsdam, from food	2.0 (0.7-5.9)	1.9 (0.6-7.6)	26
Germanyb): Heidelberg, from food	2.0 (0.5-6.6)	2.2 (0.6-8.0)	26

[a]: 2.5%-97.5%; [b]: 10%-90%

BETA CAROTENE

Table 3: Results of usage survey for β-carotene as a coloring [27]

Foodstuff	Typical use level β-carotene (mg/kg)	Range β-carotene (mg/kg)	Use
Butter [a]	2.0	2.0 - 3.6	Occasionally used for winter milk colour standardisation. Not considered a significant use of β-carotene
Margarine, other fat emulsions [a]	5.0	3 - 10	Used in most margarines/spreads
Non-alcoholic flavoured drinks [b]	2.0	2.0 - 5.0	Yellow/orange drinks only. Only 15 % of the EU market is orange flavoured.
Desserts including	4.0	4.0	Yellow/orange variants, milk-based puddings

[a] Annex III [b] Annex V Part 2

Table 4: β-carotene plasma levels in men in Europe (µmol/L, mean and standard deviation) [29]

European Region	β-carotene
Varese/Turin, IT (n=99)	0.42 ± 0.25
Florence, IT (n=97)	0.39 ± 0.21
Ragusa/Naples, IT (n=92)	0.39 ± 0.22
Athens, GR (n=95)	0.40 ± 0.21
Granada, ES (n=97)	0.24 ± 0.13
Murcia, ES (n=99)	0.25 ± 0.14
Northern Spain, ES (n=97)	0.21 ± 0.15
UK vegetarians, UK (n=99)	0.53 ± 0.47
Cambridge, UK (n=98)	0.41 ± 0.23
Potsdam, DE (n=98)	0.37 ± 0.23
Heidelberg, DE (n=99)	0.48 ± 0.62
The Netherlands, NL (n= 97)	0.29 ± 0.20
Denmark, DK (n=99)	0.31 ± 0.26
Malmö, SE (n=99)	0.30 ± 0.29
Umea, SE (n=99)	0.37 ± 0.23

Safety

β-carotene is an effective and safe source of vitamin A in both foods and food supplements and has a long history of safe use in these products. The only observed adverse effect of β-carotene in higher dosages (approx. 20 mg and above) is yellowing of the skin (carotenodermia). This is caused by the deposition β-carotene in the skin. The yellow colour disappears once β-carotene intakes are reduced.[30]

Results from two studies carried out with high risk populations led to the conclusion that daily doses of 20 mg supplemental β-carotene have harmful effects on heavy long-term smokers.[31,32] Although these results cannot be extrapolated to other populations, other dosages of β-carotene, or other combinations of nutrients, most regulatory agencies expressed safety concerns regarding high dose supplementation.

The UK Expert Committee on Vitamins and Minerals (EVM) recommends a Safe Upper Level for supplementation of 7 mg/day over a lifetime period, and recommends that, as a matter of prudence, smokers and those exposed to asbestos should not take β-carotene supplements.[33, 34] Other agencies such as the European Food Safety Agency (EFSA, formerly SCF) and the US Food and Nutrition Board (FNB) did not define an upper level due to lack of data.[1, 21] The D-A-CH group (the Nutrition Societies of Germany, Austria, and Switzerland) concluded that a daily intake of up to 10 mg of β-carotene is safe.[2] The US Council for Responsible Nutrition (CRN) recommends an upper intake level of 25 mg/d for nonsmokers and no supplementation for smokers.[35] It is noteworthy that in the "Physicians' Health Study", which was the longest of the intervention trials, no harm from β-carotene supplementation with 50 mg every other day over 12 years was reported.[36] Supplemental β-carotene of up to 50 mg/day for several years had a modest antioxidant effect even in smokers that renders a pro-oxidant effect very unlikely.[37]

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LYCOPENE

Lycopene provides the familiar red colour to tomatoes and tomato products and is one of the common carotenoids in the human diet and in human tissues. In concert with other dietary carotenoids it serves as an antioxidant in the human body and can help prevent tissue damage from free radical formation. High intake of lycopene and/or tomato products is associated with a reduction in risk of prostate cancer and of cardiovascular disease.

Lycopene is an acyclic carotenoid with 11 linearly arranged conjugated double bonds. It lacks the β-ionone ring structure and therefore has no provitamin A activity (Figure 1). Lycopene is a lipophillic compound and is insoluble in water. It is a red pigment and absorbs light in the visible range.

Figure 1

Importance for health

Antioxidant effects

Lycopene has antioxidant functions *in vitro* and *in vivo.*[1] Studies *in vitro* show that it is an excellent singlet oxygen quencher.[2] It is about twice as effective as β-carotene in protecting lymphocytes from NO_2 radical death and membrane damage.[3] It is also a peroxyl radical scavenger. Moreover, it may have an indirect antioxidant effect by inducing endogenous antioxidant defence enzymes like glutathione peroxidase, glutathione-S-transferase, and glutathione reductase.[4] In addition, lycopene can induce gap-junctional intercellular communication and affect cell proliferation.[5] In a recent 8 week human intervention trial with healthy subjects it has been demonstrated that supplementation of 12 mg lycopene/day or a mixture of lycopene with β-carotene and lutein (4 mg/day each) can significantly decrease oxidative DNA damage of human lymphocytes.[6]

Reduction of cancer risks

In recent years, studies *in vitro* and *in vivo* with tomato products and lycopene have shown promise for the prevention of certain cancer types, in particular prostate cancer.

Prostate cancer

Lycopene effectively inhibits the growth of prostate cancer cells *in vitro.*[7,8] A combination of lycopene with vitamin E seems even more effective in inhibiting prostate cancer cell growth than lycopene alone.[9] This combination also effectively suppresses growth of human prostate cancer cells in mice and increases animal's survival time.[10]

Human studies that have examined tomato product or lycopene intake or circulating lycopene concentrations in relation to prostate cancer risk can be broken down into those that support a statistically significant inverse association (6 studies); those that show a reduction in risk by about 30% but that were not statistically significant (3 studies); and those that are non supportive (7 studies).[11] The latter studies include at least 3 studies where intake of bioavailable lycopene was most likely too low to be informative.[11] It was concluded that, in view of the potential benefit for prostate health, increased consumption of tomatoes and tomato-based products might be prudent.[12]

Recently a number of intervention studies with tomato oleoresin or lycopene capsules have been carried out in prostate cancer patients. The studies (3 weeks to 2 years) carried out on patients with various types of prostate cancer all suggest that tomato oleoresin / lycopene supplementation (in the range from 4 to 30 mg/day) may decrease the growth of prostate cancer. Studies showed increased levels of lycopene in prostate tissue. Also decreased prostate tissue and leukocyte oxidative DNA damage were reported and decreased serum prostate-specific antigen (PSA) levels.[11]

Lycopene, along with other dietary carotenoids, serves as an antioxidant in the human body and can help prevent tissue damage from free radical formation.

Cancers of the digestive tract

Reviews on the available data indicated that the majority of the studies on gastric cancer (all case-control studies) showed an inverse association between tomato consumption and risk of gastric cancer, but not all were significant and still a number of studies showed no effect.[13] Also for colon and rectal cancer or other forms of cancer of the digestive tract there is emerging evidence on an inverse relationship between intake of tomato products and reduced risk of colon and rectal cancer, but this is still not conclusive.

Heart health

In a multi-centre study in 10 European countries, lycopene concentration in adipose tissue was associated with a lower risk of coronary heart disease indicating a possible protective effect from lycopene containing foods.[14] Furthermore beneficial effects on resistance of LDL to oxidation after supplementation with tomato products or lycopene[15,16] and LDL-cholesterol lowering properties by high doses of lycopene (60 mg/day) have been demonstrated.[17]

Skin protection

Exposure of the skin to UV light results in skin injury. Reactive oxygen species and other free radicals that can seriously damage membranes, proteins, and DNA and RNA seem to play an important role in this adverse event.[18] Carotenoids are suitable photoprotectants, and ß-carotene supplements are used for protection against UV light-induced erythema. Combinations of ß-carotene with lycopene and lutein but also lycopene alone (from tomato sources or synthetic) showed protective effects on UV-induced erythema in humans.[18,19,20] Carotenoids such as lycopene cannot replace a sunscreen, but may confer some basal protection and thus may contribute to defence against UV-dependent skin damage.

LYCOPENE

Food sources

The main sources of lycopene are tomatoes and tomato products followed by watermelon, papaya, pink guavas, pink grapefruit, apricots and rosehip (Table 1). Tomato products are by far the most relevant sources of lycopene in the daily diet. The lycopene content is lowest in raw tomatoes and higher in processed products such as tomato sauce or tomato paste.

In unprocessed tomato products, about 95% of lycopene is present in the all-trans form. Processing of tomatoes such as cooking, freezing or canning does not significantly change the total lycopene content but results in conversion of all-trans lycopene to various cis-isomers, mainly 5-cis, 9-cis and 13-cis lycopene.[21,22] The extent of isomerisation depends on the duration and temperature of processing, the presence of oxygen, antioxidants, moisture, and the dehydration technique applied. In commercial tomato products cis-isomers account for up to 10% of total lycopene with occasional percentages as high as 33%.[21] During storage of processed tomato products in the absence of oxygen, lycopene is stable.[21]

In addition to tomato lycopene there are also sources of synthetic lycopene and lycopene from microorganisms available as dietary ingredients or food colourant that can be added to foods or food supplements.

Table 1. Lycopene content of various foods [3,23] (means and ranges of means)

Food	Lycopene (mg/100 g wet weight)
Tomatoes, fresh	0.9 - 4.2
Tomatoes, cooked	3.7
Tomato paste	5.4 - 150
Tomato sauce	6.2
Tomato soup, condensed	8
Tomato powder, drum or spray dried	112 - 126
Tomato juice	5 –11.6
Sun-dried tomato in oil	46.5
Pizza sauce, canned	12.7
Ketchup	9.9 – 13.4
Apricot	<0.01
Apricot, canned	0.06
Apricot, dried	0.9
Grapefruit, raw pink	3.4
Guava, fresh	5.4
Guava, juice	3.3
Watermelon, fresh	2.3 – 7.2
Papaya, fresh	2.0 – 5.3
Rosehip[23]	12.9 – 35.2

Absorption and metabolism

The main factors affecting bioavailability of lycopene are the source, food processing, dietary fat, and factors interfering with absorption. In raw tomatoes, lycopene is present in crystalline form in the chromoplast[21] and the crystalline nature may account for the apparently low absorption efficiency.[24] Heating of tomato juice in oil results in a two to threefold higher bioavailability compared with untreated juice.[25] Hence, tomato products like tomato and spaghetti sauce, tomato soup, ketchup, and tomato paste are better sources of bioavailable lycopene than are fresh tomatoes.[26] About 5 g fat is essential for an efficient absorption. Thus, lycopene from tomato juice consumed in between meals is not absorbed at all. Bioavailability of synthetic lycopene has been shown to be comparable with lycopene enriched tomato oleoresin.[27] A variety of dietary factors and drugs interfere with lycopene absorption, e.g. dietary fibre, fat substitutes, plant sterols and cholesterol lowering drugs.

Pure crystalline lycopene obtained by chemical synthesis is highly sensitive to oxygen and light. Therefore, for use as a food colour, dietary ingredient or supplement it has to be stabilised by formulating with suitable carriers, antioxidants and encapsulation materials. Customary formulations containing 10% lycopene are usually stable over several months under appropriate storage conditions.[28]

Digestion and absorption of lycopene proceed in several consecutive steps. The initial step is the release from the food matrix. Being a fat-soluble compound, lycopene is then solubilized in the aqueous environment of the intestinal chyme with the help of bile salts and incorporated into mixed micelles. These mediate transfer across the unstirred water layer and uptake into the enterocyte by passive diffusion.[3] The presence of fat is essential for lycopene absorption, because fat stimulates the secretion of bile acids from the gall bladder and is required for the formation of stable micelles. In the intestinal mucosa lycopene is incorporated into chylomicrons and released into the lymphatic system and subsequently into the blood stream. In the liver lycopene is incorporated into nascent lipoproteins, which are secreted into the blood stream and act as a transport vehicle for lycopene to other tissues. Lycopene is predominantly found in the testes, adrenals, liver, adipose tissue, prostate gland, kidneys and ovaries.[3,29]

Lycopene concentrations in blood vary widely. Mean concentrations in different populations range from about 50 to 900 nmol/L and generally reflect the consumption of tomato products.[3] Typical plasma concentration levels of lycopene in men in different European regions are listed in Table 2.

While about 95% of lycopene in the diet is present in the all-trans form, cis-lycopene isomers contribute one to two thirds of total lycopene in plasma and in most tissues.[30,31] Between 10 and 20 different cis isomers are typically observed in human blood.[32,33] Little is known about the metabolism of lycopene in humans. Few oxidative metabolites have been identified in human blood and tissues.[34,35] Lycopene metabolism and degradation in rats is stimulated by testosterone.[34,36]

Most dietary lycopene is excreted via the stool. Due to its lipophilic nature lycopene is not found in urine. It is assumed that bile and stool are the main excretion routes for lycopene metabolites.[3]

Table 2: Lycopene plasma levels in men in Europe (µmol/L, mean and standard deviation)[37]

European Region	Lycopene
Varese/Turin, IT (n=99)	1.03 ± 0.43
Florence, IT (n=97)	1.01 ± 0.37
Ragusa/Naples, IT (n=92)	1.29 ± 0.46
Athens, GR (n=95)	0.90 ± 0.38
Granada, ES (n=97)	0.69 ± 0.40
Murcia, ES (n=99)	0.66 ± 0.30
Northern Spain, ES (n=97)	0.53 ± 0.31
UK vegetarians, UK (n=99)	0.98 ± 0.45
Cambridge, UK (n=98)	0.72 ± 0.30
Potsdam, DE (n=98)	0.60 ± 0.30
Heidelberg, DE (n=99)	0.62 ± 0.31
The Netherlands, NL (n= 97)	0.54 ± 0.33
Denmark, DK (n=99)	0.58 ± 0.34
Malmö, SE (n=99)	0.46 ± 0.24
Umea, SE (n=99)	0.56 ± 0.37

LYCOPENE

Intake

Intake from foods

In Europe, mean intake of lycopene ranges from about 0.5 to 5 mg/day, with high mean intakes up to 7.5 mg/day (Table 3). Intake varies with food habits and also with the method of assessment (e.g. food frequency questionnaires, diet history questionnaires, 24-h recall or household purchases). Food frequency questionnaires for example are thought to overestimate food and vegetable consumption. Note that in individuals consuming large amounts of tomato products, lycopene intake can be several fold the mean intake (e.g. 20 mg/day and more).[38] Mean intake in North America does not materially differ from that in Europe.

Intake from foods containing lycopene as colouring agents and from food supplements

Table 3. Intake of lycopene in Europe and North America

Country	Daily intake, mg	Ref
Netherlands	1.05 ± 1.56 (men)** 1.33 ± 1.88 (women)**	39
Netherlands	4.85 (2.79-7.53)***	40
Britain	1.03*	23
United Kingdom	5.01 (3.2-7.28)***	40
Spain	1.54 (0.50-2.64)***	40
Italy	7.5 (± 3.5)**	41
Ireland	4.43 (2.73-7.13)***	40
France	5.01 (3.2-7.28)***	40
France	2.8*	42
Finland	0.70* (women) 0.85* (men)	43
Germany	0.55*	44
Canada	6.3±11.8** 1.3 (median)	45
Canada	25.2*	46
United States	1.1 ± 7.2 to 9.4 ± 0.28 ****	45

* mean
**mean ± standard deviation
*** interquartile range
**** range of means ± standard deviations reported for epidemiologic studies

Lycopene from various approved sources (synthetic, from red tomatoes or Blakeslea trispora) is allowed to be added to various foods, including for several food categories, including non-alcoholic beverages, bakery products, ice cream, desserts, fish products, meal replacements and food supplements, for coloring purposes under EU additive rules.

Synthetic lycopene can also be used as a nutrient as it received an authorisation as a novel food ingredient for a range of foods and in food supplements. Products in the market (in particular in the USA) contain between 5 and 20 mg lycopene per recommended daily dose. Multiple-component supplements targeted at prostate health contain 3 to 5 mg lycopene per daily dose. Some multi-vitamin supplements also contain lycopene at doses ranging from 0.3 to 1 mg per day.

Recommended intakes

No Dietary Reference Intake for lycopene has been established. However several human intervention trials indicate that lycopene may play an important role in protection of cellular functions against oxidative damage.

Safety

There are no signs of any significant adverse biological effect by lycopene (even at high doses), neither from the numerous epidemiological studies nor from clinical studies evaluating various endpoints upon lycopene supplementation through protocols using tomato-based products or tomato-based capsules. The only side effect that might be observed with a long-term intake of relatively high doses (dose needed unknown) is lycopenodermia (carotenodermia), a harmless and reversible discolouration of the skin.[3]

Using established risk assessment procedures for nutrients for which a Tolerable Upper Intake Level (UL) could not be derived, an Observed Safe Level (OSL) of 75 mg/d has been suggested for lycopene.[47]

In the EU, several new forms of lycopene have been approved as novel foods for addition to foods in recent years.

More recently, the European Food Safety Authority (EFSA) derived an ADI of 0.5 mg/kg bw/day based on a No-Observed-Adverse-Effect Level (NOAEL) of 50 mg/kg bw/day from a one-year rat study and a non- reversible increase in serum alanine transaminase (ALT) activity.[48,49,50] In 2009 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) replaced the group ADI of 0-0.5 mg/kg bw with a group ADI "not specified" for lycopene from all sources.[51]

The JECFA evaluation also included the one-year rat study and described the effects on aspartate transaminase (AST) and ALT activities. These different interpretations, based on the same data present a problem for risk managers.

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LUTEIN AND ZEAXANTHIN

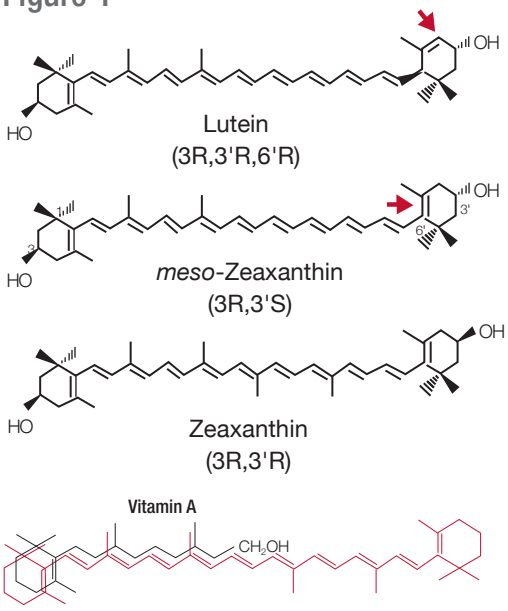
Lutein and zeaxanthin are members of the large group of carotenoids, which are lipophilic plant pigments responsible for the yellow to red colours in nature, as in fruit, vegetables, flowers, and autumn leaves. For example, the bright yellow colour of corn (maize) is due to lutein and zeaxanthin.

Based on their chemical composition, carotenoids can be divided into hydrocarbons – carotenoids comprising only carbon (C) and hydrogen (H), such as β-carotene or lycopene – and into xanthophylls. The latter contain oxygen (O), in addition to carbon and hydrogen. Lutein and zeaxanthin belong to the group of xanthophylls.

Further, carotenoids can be distinguished into those with provitamin A activity, and those without provitamin A activity. Lutein and Zeaxanthin do not have any provitamin A activity, i.e. they cannot be used by humans as a source of vitamin A.

Interest in lutein and zeaxanthin is focusing on their role in the eye: they are the only two dietary carotenoids highly and selectively accumulated in the retina, especially in the macula lutea, the site of highest visual acuity. There, lutein and zeaxanthin together with meso-zeaxanthin, a lutein/zeaxanthin stereoisomer that originates from lutein metabolism within the retina, compose the macular pigment (MP), protecting the retina against light-induced damage, and thus contributing to healthy vision throughout life (Figure 1 for the molecular structures of β-carotene, vitamin A (retinol), lutein, zeaxanthin, and mesozeaxanthin).Because lutein and zeaxanthin are not synthesized in the body, they must be acquired from the diet either through foods or dietary supplements.

Figure 1



Importance for health

The roles of lutein and zeaxanthin in humans may be considered both in terms of 'generic' effects – effects displayed by all other carotenoids – and in terms of effects specific to lutein and zeaxanthin.

General health benefits

Similar to all carotenoids, lutein and zeaxanthin are effective antioxidants, protecting important biomolecules and cells against damage induced by free radicals. Lutein and other carotenoids are proven to act as antioxidants in blood[1] and to reduce the skin´s sensitivity against UV-induced erythema ('sunburn').[2] Further, as diets high in fruit and vegetables provide lutein and zeaxanthin, these two carotenoids contribute to the health benefits observed with such diets, for example in relation to heart disease and cancer.[3]

Eye health

Lutein and zeaxanthin are found in almost all the structures of the eye. They are the only two dietary carotenoids selectively concentrated in the retina and in particular in the macula lutea, the region of the retina responsible for central vision and visual acuity, and in the lens. None of the other carotenoids typically found in blood and tissues are present in retina and lens. Lutein and zeaxanthin act as antioxidants and as blue-light filters. It is because of these specific features that lutein and zeaxanthin have been associated with healthy vision throughout life, with beneficial effects in two age-related eye diseases - age-related macular degeneration (AMD) and cataract – and with possible improvement in visual performance.

AMD

The localization of the MP within the retina - like a shield between incoming light and the photoreceptors - and its capacity to act as antioxidant and absorb blue light makes it ideal for protection. Blue light is the part of the visible light spectrum with the highest energy and ability to generate reactive oxygen species (ROS), and the retina has long been known to be especially vulnerable to blue light ('blue light hazard'). Antioxidant protection is



Lutein and zeaxanthin are selectively accumulated in the macula lutea and protect the retina against light-induced damage.

critically important to the eye: due to its high level of exposure to light, all structures in the eye are at high risk of damage from light induced free radicals. High levels of blood (and thus oxygen) supply, together with the high levels of polyunsaturated fatty acids in photoreceptor membranes make the retina even more susceptible to oxidative damage. Indeed, high levels of lutein and zeaxanthin in the retina have been demonstrated to protect photoreceptor cells against light-induced damage.[4]

AMD affects the macula lutea, the centre of the retina and site of highest visual acuity, needed for activities such as reading. AMD is characterised by progressive loss of central vision and is the leading cause of irreversible blindness in western countries. Currently, there is no cure, and only a few treatment strategies, mainly addressing the more severe form of the disease (wet AMD), are available. The main risk factor for AMD is age. Thus, options for prevention appear very important, especially in the ageing western societies.

The rationale for the MP - lutein and zeaxanthin – in prevention of AMD is based on the idea that high MP optical density (MPOD) throughout life reduces damage to retinal structures which would otherwise accumulate over decades and become manifest as symptoms of AMD later in life. Strong support comes from data on primates who were raised on a diet devoid of lutein and zeaxanthin: lutein and zeaxanthin levels in blood and tissues were not detectable in these animals. Further, they did not develop a macular pigment, but experienced changes in the retina which were similar to those observed in the early stages of AMD.[4]

In humans, lower MPOD has been observed in AMD patients as compared to healthy controls, and this was established to be the cause of the disease, rather than its consequence.[4] Additional data from epidemiological studies suggest lower disease risk with higher intakes and/or higher blood levels of lutein and zeaxanthin, although such associations were not observed in all studies.[5,6] However, the relations between intake, blood levels and levels in the macula MPOD are complex, and correlations between these parameters are poor, so that absence of associations between lutein and zeaxanthin and AMD risk in epidemiologic studies may be due to confounding factors concealing this association.[7] A recent report from the AREDS[i] study group reinforces the inverse association between the dietary intake of lutein and zeaxanthin and the risk of advanced, neovascular (NV) AMD, geographic atrophy (GA) and / or presence and enlargement of drusen in human eyes.[8]

Intervention studies confirmed that the supplementation with lutein/zeaxanthin over a period of 6 to 12 months results in increased MPOD and helps to improve visual and macular function in AMD patients.[9,10,11]

Evidence on the effects of long term supplementation with lutein and zeaxanthin on reducing the progression of advanced AMD is currently being investigated in Age-Related Eye Disease Study 2 (AREDS2), a clinical trial conducted by the National Eye Institute of the US National Institutes of Health (NIH) whose results are expected by 2013.[12]

i AREDS: Age-Related Eye Disease Study

Cataracts

Lutein and zeaxanthin are the only dietary carotenoids also accumulating in the lens.[13]

Epidemiological studies suggest a reduced risk for prevalence of cataract or cataract extraction with high intakes or serum levels of lutein and zeaxanthin, when compared to low intake or blood levels. [6,14,15,16] Further, there is a relation between clarity of the lens and MPOD: in people above 50 years of age, a clearer lens was related to higher MPOD, suggesting that lutein and zeaxanthin in the eye may retard ageing of the lens.[17,18] Additional evidence for the beneficial role of dietary lutein and zeaxanthin on reducing the risk of cataracts comes from a US study published in January 2008 showing that women in the highest quintiles of dietary lutein and zeaxanthin (consuming an average of 6.7 mg/day) had 18% lower risk of cataract compared to women in the lowest quintile (1.2 mg/day on average).[19]

LUTEIN AND ZEAXANTHIN

The scientific evidence for the beneficial role of lutein and zeaxanthin in cataracts mainly comes from observational studies and more prospective, randomized, placebo-controlled clinical trials are needed to confirm this relationship. In this respect, important support will be provided by the AREDS2 study which also aims to assess the effect of the long term supplementation with the two xanthophylls on cataracts.

Visual function

The physicochemical features of lutein and zeaxanthin, more specifically the blue-light absorption characteristics, imply that they may have 'short term effects', i.e. effects on measures of visual function, such as visual acuity, glare and contrast sensitivity.[20] Data from some pilot trials and a one year placebo-controlled human intervention trial proved that these effects do occur: MPOD increased, and visual acuity and contrast sensitivity improved.[9]

Evidence is also accumulating on the efficacy of lutein and zeaxanthin supplementation and the subsequent increase in serum concentrations and MPOD in young healthy adults.[21,22]
A recent paper showed that 6 months intake of lutein and zeaxanthin increased MPOD and improved visual performance under glare conditions.[23] Macular pigment density increase was strongly related to improvements in glare disability and photostress recovery. Another intervention trial reported improved visual function especially in contrast sensitivity in subjects who received lutein suggesting that intake of lutein may have beneficial effects on visual performance.[24]

It has further been reported within a randomized, controlled, double-blind trial that lutein supplementation could help to reduce symptoms of visual fatigue.[25]

Skin health

The skin is the second largest repository of lutein in the body.[26]

The scientific literature contains numerous articles that address the beneficial effects of lutein and zeaxanthin combined with other carotenoids or antioxidants such as β-carotene, lycopene, vitamin C, vitamin E, alpha-lipoic acid, and/or selenium in human skin.[2,27,28]

Morganti P et al.found that carotenoids used as nutritional supplements seemed to play an interesting photoprotective role for both skin and eyes, eventually increasing the activity of topical sunscreens.[29]

Heinrich U et al.found that the administration of antioxidant supplements composed of carotenoids (lycopene, lutein and β-carotene), vitamin E and selenium during 12 weeks improved parameters related to skin structure – skin density, skin thickness and roughness - in humans.[30]

In a randomized, double-blind, placebo-controlled study Palombo P et al. evaluated the effect of oral, topical or combined oral/topical administration of lutein and zeaxanthin during 12 weeks on 5 skin health parameters: skin elasticity and hydration, skin lipid and lipid peroxidation and skin photoprotective activity. [31]
No additional carotenoids or antioxidant were administered to the study participants. The study found that oral, topical and combined lutein and zeaxanthin improved all the parameters evaluated. The combined oral and topical administration of lutein and zeaxanthin overall provided the highest degree of antioxidant protection. In addition, oral administration of lutein may provide better protection than that afforded by topical application of this antioxidant when measured by changes in lipid peroxidation and photoprotective activity in the skin following UV light irradiation.

Food sources

Lutein and zeaxanthin are not synthesized in the body so they must be acquired from the diet either through foods or dietary supplements.

Lutein and zeaxanthin occur in nature as yellow pigments in vegetables, fruit and flowers. Dark green leafy vegetables such as kale, spinach and broccoli have been identified as some of the best sources. Other rich sources are sweet corn, yellow peppers and pumpkins, and lutein also occurs in egg yolks, grains and potatoes (Table 1).

Table 1: Lutein and zeaxanthin content in selected foods (mg/100g)

	Lutein*	Zeaxanthin
Kale	14.7 – 39.6	n.a.
Spinach	4.5 – 15. 9	0.2 – 0.3
Broccoli	0.8 – 2.4	n.a.
Peas	1.1 – 2.4	n.a.
Corn	0.4 – 1.9	0.3 – 0.9
Carrots	0.2 – 0.3	n.a.
Pepper (yellow/red)	< 0.1 – 8.2	1.5 – 16.8
Oranges	0. 1 – 0.2	0.07
Peaches	< 0.1	< 0.01
Apples	< 0.1	< 0.01
Eggs	0.1 – 2.1	0.1 – 1.6
Potatoes	0.02 – 0.05	< 0.01 – 0,11
Grains	0.02 – 0.14	< 0.01 – 0.03

*For analytical reasons lutein and zeaxanthin are often reported together.
n.a. not available

In nature, both lutein and zeaxanthin occur in 'free' form – as in green vegetables – and in the form of their fatty acid esters, usually in flowers and low concentrations in yellow to orange vegetables and fruit.

Marigold flowers (Tagetes erecta) have been the source of commercial lutein preparations since the late 1960s. These have a long history of use in animal feed, where they are added to the feed of chicken to enhance the colour of both egg yolks and skin, the latter being desirable for an attractive appearance of roasted chicken. Lutein extracts from Tagetes are also approved as food colour (E 161b), the main uses being in dairy products, non-alcoholic drinks, bakery products and ice-cream. Highly purified marigold extracts, either containing 'free' lutein or lutein esters, are also marketed as ingredients for food supplements and fortified foods for the beneficial effects of lutein on human health. All commercial marigold-derived lutein preparations contain 5 – 10% zeaxanthin, due to its natural presence in marigolds.

Absorption and metabolism

The absorption of lutein and zeaxanthin follows the same pathway as that of all other fat soluble dietary compounds – for example, triglycerides, cholesterol, vitamin E – i.e. fat is necessary for proper absorption.

Lutein esters have to be hydrolysed (cleaved) prior to absorption, since only the free lutein is absorbed and appears in blood.

In brief, lutein and zeaxanthin are incorporated into micelles formed with dietary fats and bile acids in the small intestine, and taken up into the cells lining the intestinal wall. There, lutein and zeaxanthin are incorporated into chylomicrons which transport the newly absorbed carotenoids via the lymph into the blood circulation and to the liver for incorporation into other lipoproteins. In blood, lutein and zeaxanthin are transported in lipoproteins – in both LDL and HDL - to target tissues.

Adipose tissue and liver may be regarded as storage sites.

Lutein and zeaxanthin are two of the six major carotenoids found in human blood. Their blood concentrations depend on dietary intake and, consequently, can be raised by increasing intake, either via diet or supplementation. However, blood concentrations achieved from a given intake of lutein depend on many other factors and will vary considerably among individual people. In Europe, typical concentrations in blood are around 0.4 µmol/L for lutein and 0.1 µmol/L for zeaxanthin (see also Table 2), with high variation due to dietary habits and other factors.[32]

Table 2: Lutein and Zeaxanthin Plasma Levels in Men in Europe (µmol/L, mean and standard deviation)[32]

Site	Lutein	Zeaxanthin
Varese/Turin, IT (n = 99)	0.60 ± 0.24	0.13 ± 0.06
Florence, IT (n = 97)	0.56 ± 0.21	0.11 ± 0.06
Ragusa/Naples, IT (n = 92)	0.61 ± 0.26	0.11 ± 0.05
Athens, GR (n = 95)	0.51 ± 0.21	0.11 ± 0.04
Granada, ES (n = 97)	0.40 ± 0.16	0.10 ± 0.04
Murcia, ES (n = 99)	0.37 ± 0.17	0.11 ± 0.05
Northern Spain, ES (n = 97)	0.36 ± 0.15	0.12 ± 0.05
UK vegetarians, UK (n = 99)	0.38 ± 0.17	0.09 ± 0.05
Cambridge, UK (n = 98)	0.26 ± 0.12	0.06 ± 0.04
Potsdam, DE (n = 98)	0.27 ± 0.13	0.07 ± 0.03
Heidelberg, DE (n = 99)	0.29 ± 0.12	0.08 ± 0.04
The Netherlands, NL (n = 97)	0.28 ± 0.12	0.07 ± 0.03
Denmark, DK (n = 99)	0.28 ± 0.13	0.05 ± 0.03
Malmö, SE (n = 99)	0.28 ± 0.13	0.06 ± 0.03
Umea, SE (n = 99)	0.27 ± 0.11	0.05 ± 0.02

LUTEIN AND ZEAXANTHIN

Absorption and metabolism continued

Functional, highly selective accumulation occurs in the macular region of the retina of the eye and to a lesser extent, in the lens.

Concentration in the centre of the retina, the site of highest visual acuity, is so much higher that lutein and zeaxanthin are macroscopically visible and have given the centre of the retina its name: Macula lutea, which is latin for 'yellow spot'. Lutein and zeaxanthin in the macular region are also termed 'macular pigment', and the amount of macular pigment is referred to as 'macular pigment optical density' or 'MPOD'. Today, it is established that the macular pigment consists solely of lutein, zeaxanthin and meso-zeaxanthin (see Figure 1 for structural formulas).

Meso-zeaxanthin is derived from lutein and is found exclusively in the macula and retina of the eye.[33]

The levels of lutein and zeaxanthin – the MPOD – can be modified by changing the intake of lutein and zeaxanthin, with dietary measures as well as by supplementation.[4]

Intake

Most food composition tables do not separate lutein and zeaxanthin, but report them together. However, lutein is more abundant in the human diet, and zeaxanthin intakes have been reported to be 0.1 – 0.2 mg/day, i.e. approximately 10% of the lutein intakes.[34] A diet rich in vegetables and fruit could supply an adequate level of lutein per day. Individual lutein intakes however vary greatly depending on individual dietary patterns.

Since the macular xanthophylls are exclusively of dietary origin and the mean intake of lutein and zeaxanthin from the modern western European diet ranges only from 1.56 to 3.25 mg/person/day depending on the country where people live, increased consumption of lutein and zeaxanthin is recommended.[35] Table 3 gives typical lutein intakes in various European countries.

Table 3. Lutein intakes in Europe (mg/day)[35]

Country	Median	Range (interquartile range*)
Spain (n = 70)	3.25	1.75 – 4.34
France (n = 76)	2.50	1.71 – 3.91
UK (n = 71)	1.59	1.19 – 2.37
Republic of Ireland (n = 76)	1.56	1.14 – 2.1
The Netherlands (n = 75)	2.01	1.42 – 3.04

*Interquartile range: statistical parameter, describing the difference between upper quartile (Q_3, 75th percentile) and lower quartile (Q_1, 25th percentile), i.e., the lowest 25% of intakes and the highest 25% of intake are not included.

Recommended intakes

No dietary reference intakes (DRIs) or recommended dietary allowances (RDAs) have yet been set for lutein or zeaxanthin, because such values exist only for vitamins and minerals and other essential nutrients. Based on data on beneficial effects observed in some epidemiological studies, intakes of at least 6 mg lutein/day seem desirable for healthy people.[5]

Increases in MPOD have been observed – although not in all individuals – with supplemental intakes as low as 2.4 mg lutein given daily over a period of several months.[36] Beneficial effects of lutein supplementation on increased serum levels and MPOD and improvement of various parameters of visual performance were observed in patients with early forms of AMD or in healthy subjects with 10 mg lutein/day.[21,33] This level of intake was also chosen by the investigators of the AREDS2 trial.[12]

Newborn babies get their lutein and zeaxanthin from their mother's milk. Compared to breast milk, lutein and zeaxanthin levels in commercial infant formulas are usually much lower[37] if not completely absent, and it has been hypothesised whether inadequate supply of lutein and zeaxanthin early in life may have serious conequences.[38]

Safety

The long history of consumption of foods rich in lutein and zeaxanthin provides evidence that these carotenoids are safe. In addition, no adverse effects have been observed in intervention studies involving supplementation with high doses of lutein (up to 40 mg/day) for extended periods of time.[9,39,40]

Both lutein and lutein esters have completed the GRAS (Generally Recognized As Safe) self-affirmation as well as the GRAS notification process according to the requirements of the US FDA. This includes a formal safety assessment by scientific expert panels. Furthermore, after assessing similar information, the Joint Expert Committee on Food Additives of the FAO/ WHO[ii] (JECFA) established an acceptable daily intake (ADI) level for lutein and zeaxanthin of up to 2 mg/kg bw.

The European Food Safety Authority (EFSA) recently established an ADI of 1 mg/kg bw/day. This ADI is based on the NOAEL of 200 mg/kg bw/day (the highest dose level tested) in a 90-day rat study. Given the absence of a multigeneration reproductive toxicity study and of chronic toxicity/carcinogenicity studies EFSA applied an uncertainty factor of 200.[41]

Using recently developed risk assessment procedures for nutrients for which a Tolerable Upper Intake Level (UL) could not be derived, an Observed Safe Level (OSL) of 20 mg/d has been suggested for lutein.[42]

In Europe, foods and/or food ingredients which have not been consumed in significant amounts prior to May 1997 – the date when the Novel Foods Regulation came into force – need to undergo the approval process as outlined in the Regulation if they do not have a history of safe food use. Lutein and lutein esters derived from Tagetes erecta have been widely used as active ingredients in food supplements in Member States of the European Union before May 1997. Also they have a history of safe use as approved food additives in Europe and as GRAS approved food ingredients in the US. Further, a competent authority in one of the EU Member States (Agence Française de Sécurité Sanitaire des Aliments, AFSSA) authorised the use of an extract from Tagetes erecta (consisting mainly of lutein and zeaxanthin) as a food supplement ingredient thus confirming implicitly that lutein is not considered to be a novel food.[43]

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BIOACTIVE SUBSTANCES

Polyunsaturated Fatty Acids (PUFA)

Conjugated Linoleic Acid

L-Carnitine

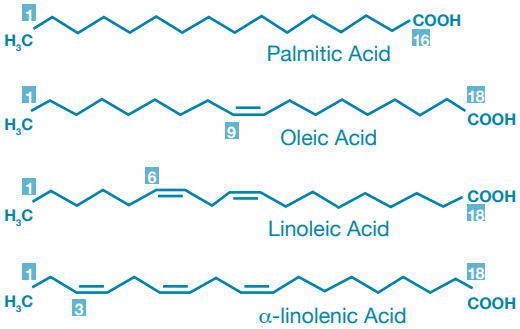
Coenzyme Q10

EGCG

POLYUNSATURATED FATTY ACIDS

Fatty acids are components of fat. They are mostly bound or attached to other molecules, such as in triglycerides or phospho-lipids. When they are not attached to other molecules, they are known as “free” fatty acids. Fatty acids (Figure 1) are linear hydrocarbon chains with a methyl (CH3-, also called the ω-end) and a carboxyl (-COOH) end.

Figure 1: Chemical structures of saturated, monounsaturated and polyunsaturated fatty acids (the carbon atoms are numbered beginning at the methyl end)



Introduction

Fatty acids vary in their number of carbon atoms and double bonds and are classified as follows:[1]

- Saturated fatty acids (SFA, no double bonds)
- Monounsaturated fatty acids (MUFA, one double bond)
- Polyunsaturated fatty acids (PUFA, two or more double bonds)
- Omega-6 PUFA
- Omega-3 PUFA

Omega-6 PUFA (also known as ω-6 PUFA, n-6 PUFA) have the first double bond at carbon number 6 counting from the methyl end. The major omega-6 PUFA in the diet are:

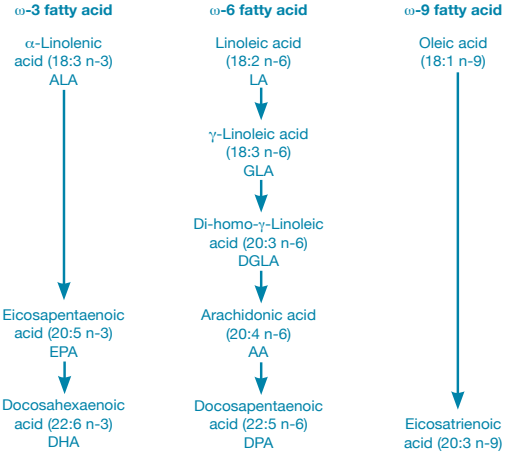
- linoleic acid (LA)
- γ-linolenic acid (GLA)
- arachidonic acid (AA)

Omega-3 PUFA (also known as ω-3 PUFA, n-3 PUFA) have the first double bond at carbon number 3 counting from the methyl end. The major omega-3 PUFA in the diet are:

- alpha-linolenic acid (ALA)
- eicosapentaenoic acid (EPA)
- docosahexaenoic acid (DHA)

Both saturated and monounsaturated fatty acids can be synthesized by the human body. Linoleic acid (LA) and α-linolenic acid (ALA) however, are essential nutrients and must be obtained from a dietary source to avoid deficiency.[2] LA can be metabolized to arachidonic acid and docosapentaenoic acid (DPA) in the human body. ALA can be transformed to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Figure 2). Recent studies demonstrate that the conversion rate to EPA and DHA is very low, so much so that it is being suggested EPA and DHA become regarded as essential themselves.[3]

Figure 2: Enzymatic conversion of different omega fatty acids



Polyunsaturated fatty acids (PUFA) are essential for health. They act as structural components of bio-membranes. For instance, omega-6 and omega-3 PUFA are important structural components of the phospholipid cell membranes of the tissues, which have multiple physiological functions.

Importance for health

Polyunsaturated fatty acids as structural components of bio-membranes

Omega-6 and omega-3 PUFA are important structural components of the phospholipid cell membranes of the tissues, which have multiple physiological functions.[4,5] The composition of the phospholipids influences cell membrane characteristics such as fluidity and permeability to other molecules. They are essential for various membrane functions such as activity of membrane-bound enzymes and receptors, and signal transduction. Here are some examples:

Skin:

Omega-6 PUFA are integral components of skin lipids.[6] LA is incorporated into skin ceramides, which is essential for maintaining the water permeability barrier of the skin. Excessive trans-epidermal water loss should be avoided.[6] A prolonged lack of dietary omega-6 PUFA has been shown to increase trans-epidermal water loss, causing rough and scaly skin, and may contribute to the development of dermatitis.[1]

Brain:

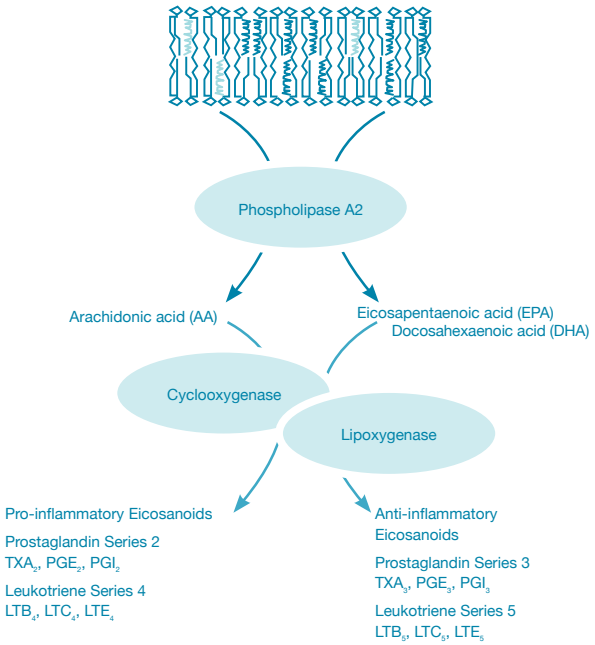
The developing brain accumulates large amounts of PUFA both pre- and postnatally. AA and DHA are the major PUFA in the brain, nervous tissue and retina.[6] DHA seems to be essential for the visual process in the retina and for proper brain functioning.[7]

Polyunsaturated fatty acids as precursors for eicosanoids

DGLA, AA and EPA give rise to eicosanoids, a group of biologically active substances that control physiologically important processes such as blood pressure, renal function, blood coagulation, inflammatory and immunological reactions.[4]

Homologous omega-6 PUFA and omega-3 PUFA compete against each other and for the same metabolic enzymes (Figure 3). For instance, EPA intake increases the tissue concentration of EPA and lowers that of AA. Concomitantly, there is a shift of eicosanoids in favour of the eicosanoids derived from EPA by having lesser inflammatory activity than those derived from AA. It has been suggested that high intakes of some omega-6 fatty acids may shift the physiological state to one that is proinflammatory and prothrombotic, characterised by high blood viscosity, vasoconstriction and short bleeding times. Long chain omega-3 PUFA (EPA, DHA), however, have anti-inflammatory, antithrombotic, antiarrhythmic, vasodilatory and triglyceride lowering properties.[8,9,10,11,12] Evidence suggests that high AA/EPA tissue ratios may play a contributory role in the development of chronic diseases in later life such as coronary heart disease and stroke, cancer or diabetes.[1]

Figure 3: Eicosanoids from AA and EPA compete against each other.



POLYUNSATURATED FATTY ACIDS

The European Food Safety Authority (EFSA) has acknowledged the following beneficial effects of polyunsaturated fatty acids as a basis for health claims:

Consumption of docosahexaenoic acid (DHA)[13,14]
- Maintenance of normal (fasting) blood concentrations of triglycerides
- Maintenance of normal brain function
- Maintenance of normal vision
- Contribution to the visual development of infants

Consumption of eicosapentaenoic acid (EPA) and Docosaheaxenoic acid (DHA)[15,16]
- Maintenance of normal cardiac function
- Maintenance of normal blood pressure
- Maintenance of normal blood concentrations of triglycerides

Consumption of linoleic acid (LA)[17]
- Maintenance of normal cholesterol concentrations

Consumption of alpha-linolenic acid (ALA)
- Maintenance of normal blood cholesterol concentrations
- Contributes to brain and nerve tissue development in infants and young children

Consumption of essential fatty acids[18]
- Normal growth and development of children

Food sources

Dietary fatty acids derive from both animals and plants (Table 1). In general, animal fats are high in saturated fatty acids. Vegetable oils tend to be higher in unsaturated fatty acids and are therefore liquid at room temperature.[1]

Rich sources of omega-6 PUFA include nuts, seeds and most oils used in the kitchen, with the exception of olive oil. Certain specialty oils, such as blackcurrant, evening primrose and borage seed oils, are high in GLA. AA is present in small amounts in meat, poultry and eggs. It is virtually absent in plant-derived fats and oils.[1]

Omega-3 PUFA are found in some vegetable oils, fish and seafood.[19] Soybean, rapeseed and walnut oils are high in ALA. DHA and EPA are found predominantly in fish and seafood and to a lesser extent in egg yolk and meat.[6] Dietary omega-6 and omega-3 PUFA are almost completely absorbed in the small intestine of healthy individuals.[7]

Table 1: Food sources of polyunsaturated fatty acids[20]

Food source	PUFA (g/100g)			Total fat (g/100g)
	Total PUFA	ω-3 PUFA	ω-6 PUFA	
Coconut oil	1.80	0	1.80	100
Corn oil	56.2	1.05	55.2	100
Olive oil	7.64	0.56	7.07	100
Rapeseed oil	33.2	11.1	22.1	100
Salmon, raw	3.36	3.01	0.36	10.0
Soybean oil, refined	60.4	6.88	53.5	100
Sunflower oil	63.0	0	63.0	100
Walnuts	43.9	7.46	36.4	64.3

PUFA supplements

Available omega-3 PUFA food supplements contain EPA and DHA derived from marine oils in varying proportions, and contain 180 mg EPA and 120 mg DHA per capsule. Typical cod liver oil supplements contain 173 mg EPA and 120 mg DHA. For vegetarians there is an alternative in the form of DHA oils derived from algae (100 mg DHA per capsule).[19]

Food fortification

Foods (e.g. bread, dairy products, dressings, meats, eggs) enriched with omega-3 PUFA (ALA, EPA and DHA) have become available and are an alternative to increase the intake of these PUFA.[6] For fortification purposes, two product forms are available: oils and powders (produced by microencapsulation technology). The powdered products can be used in baked goods, bars, cereals, dietetic products, etc. Oil emulsions are suitable for use in liquid food matrices.[19] No estimates are available on the contribution of fortified foods to the total intake of omega-6 or omega-3 PUFA, especially DHA and EPA, in Europeans.[6]

Recommended intakes

Recommendations for total PUFA intakes vary between 2.5 and 12% of the total daily energy intake (En%, Table 2). Recommendations for intakes of omega-6 PUFA and omega-3 PUFA vary between 2 - 10 and 0.5 - 2 En%, respectively. The SCF defined Population Reference Intakes (PRI) of 2 En% for omega-6 PUFA and 0,5 En% for omega-3 PUFA.[21] This corresponds to a daily intake of approximately 6 g/day and 8 g/day for a typical adult female and male, respectively. The corresponding amounts of omega-6 PUFA for women and men are 5 g/day and 6.4 g/day and for omega-3 PUFA 1 g/day and 1.6 g/day, respectively. The Nordic, D-A-CH and Dutch recommendations also apply to pregnant and lactating women. The French ANC recommends somewhat higher intakes during pregnancy and lactation.[6]

The differences in recommendations reflect different nutritional goals. The SCF[21] and D-A-CH[22] recommendations for omega-3 PUFA are based on the amounts necessary to correct clinically overt omega-3 PUFA deficiency and to which a safety allowance was added. The recommendations for total omega-3 PUFA formulated by WHO[23] were based on considerations of cardiovascular health and neurodevelopment.

POLYUNSATURATED FATTY ACIDS

There are only a few dietary recommendations for individual omega-3 PUFA or omega-6 PUFA. The Food and Nutrition Board recommends 1.6 g/d (men) / 1.1 g/d (women) of ALA.[1] In France recommendations for long-chain omega-3 PUFA (EPA, DHA) have been established (500 mg/d for men and 400 mg/d for women).[6] The WHO recommendation of 1-2 servings of fish per week corresponds to 200-500 mg of EPA and DHA.[24]

As mentioned above, omega-6 and omega-3 PUFA compete for the same enzymes. Therefore, in addition to the reference values for groups or individual fatty acids, ratios of omega-6 and omega-3 PUFA have also been recommended. As can be calculated from Table 2 the omega-6/omega-3 PUFA ratio varies between 1:1 and 10:1, depending on whether adequate or upper level values are selected. There is no consensus about the optimal omega6/omega-3 PUFA ratio in the diet.

Table 2: Recommended daily intakes of PUFA for adults as a proportion of the total daily energy intake (En%) according to different institutions[6,18]

Country	PUFA (En%)		
	Total	ω-6 PUFA	ω-3 PUFA
German-Austrian-Swiss recommendations (DGE, 2006; DACH, 2008)	3	2.5	0.5
Nutritional Recommendations for the French Population (AFSSA, 2001)	5	4	0.8
Health Council of the Netherlands (GR, 2001 and 2006)	3 – 12	2	1
Nordic Nutrition Recommendations (NNR, 2004)	≥ 5	≥ 4	1
SCF, 1993	2.5	2	0.5
UK (DoH, 1991)	6	> 1	> 0.2
USA (FNB, 2002)	5.6 – 11.2	5 – 10	0.6 – 1.2 for ALA only
WHO/FAO, 2003	6 – 10	5 – 8	1 – 2

Intake

Surveys in several European countries reported average intakes of total PUFA ranging from 3 to 7 En% (Table 3). In many countries the average PUFA intake was below 6 En%, the lower limit of the WHO recommendations.[24]

In general, dietary intakes of omega-6 PUFA are in line with the recommendations defined in Table 2. Dietary intakes of omega-3 PUFA vary with the amounts and types of vegetable oils and fish in the diet.[6] Whereas the observed intakes of total omega-3 PUFA and ALA as percent of the energy intake are close to the SCF recommendations, the intakes of long-chain omega-3 PUFA such as DHA or EPA are mostly lower than recommended by national authorities. In general, it was observed that the intake of the long-chain PUFA EPA or DHA increases with age in parallel with an increase in fish consumption.[6]

Table 3: Dietary intakes of PUFA by adults in Europe[6]

Country	PUFA (En%)					
	Total		ω-6 PUFA		ω-3 PUFA	
	M	W	M	W	M	W
Finland	5.2	4.9	4.1	3.8	1.1	1.0
Germany	4.6	4.8	-	-	-	-
Greece	6.0	7.0	-	-	-	-
Italy	5.0	-	-	-	-	
Sweden	4.6	4.7	3.7	4.0	0.7	0.7
The Netherlands	7.0	6.8	-	-	-	-
United Kingdom	6.4	6.3	5.4	5.3	1.0	1.0

Safety

Data on the safety of PUFA intakes above 10 En% are limited. No UL has been set for either omega-6 PUFA or omega-3 PUFA because no intake level could be established at which adverse effects occur.[1] The most common adverse affects include gastrointestinal discomfort and nausea. The gastrointestinal events were therefore most likely in response to the ingestion of such a large volume of an oily substance as opposed to the actual omega-3 PUFA. Very high doses (> 20 g/d) of omega-3 PUFA might be associated with increased bleeding times.[25] However moderate consumption (ranging up to 7.5 g/day) does not appear to cause this.[26] Hence in the light of current knowledge, the addition of commonly used amounts of PUFA from dietary supplements to typical dietary intakes of PUFA is within a safe range.

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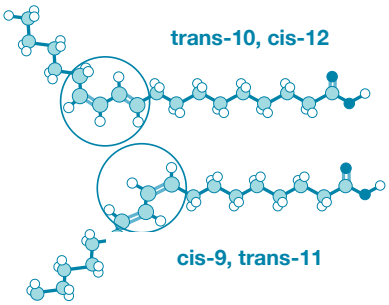
CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA) refers to a group of positional and geometric forms of conjugated isomers of linoleic acid. The conjugated double bonds can occur in either the cis or trans configuration and are present predominantly in positions 9 and 11 or 10 and 12 (Figure 1).

Figure 1: Chemical structure of conjugated linoleic acid



Introduction

Conjugated linoleic acid (CLA) is a fatty acid produced by ruminant (cud-chewing) animals, whose specialized digestive system including ruminant bacteria converts linoleic acid from feed into CLA. CLA therefore occurs naturally in animal products such as beef, milk and milk products.

Though CLA contains both trans and cis double bounds, CLA is not considered a "trans-fat". In November 2004, the Codex Alimentarius Commission agreed on the following definition for trans fatty acids: "…trans fatty acids are defined as all the geometrical isomers of monounsaturated and polyunsaturated fatty acids having non-conjugated interrupted by at least one methylene group ($-CH_2-CH_2-$) carbon-carbon double bonds in the *trans configuration*."[1] This internationally accepted definition is in line with those currently applied by regulations in Denmark[2] and the USA,[3] where the Danish and the FDA definitions of trans fatty acids expressly exclude conjugated fatty acids from the scope of their regulations. Thus, based on the international practise and internationally agreed definitions, CLA is not considered to be a trans fatty acid.

Most commercial preparations of CLA predominantly contain cis-9, trans-11 CLA and trans-10, cis-12 CLA isomers in equal amounts, and with smaller amounts of other CLA isomers.

Importance for health

Supplements composed of two isomers of CLA, the cis-9, trans-11 and the trans-10, cis-12, have been well studied in experimental models in relation to immune function, cancer, atherosclerosis, and glucose maintenance. One of the most widely reported effects of 50:50 CLA-mix is its influence on body composition. Body composition is the technical term used to describe the different body compartments (lean mass, fat mass, body water and bone mass) that make up a person's body weight.

The effect of CLA-mix is mainly on reducing body fat and improving body composition that may not necessarily be accompanied by weight loss. An optimal body composition is more critical to long-term health than just weight loss. In fact, obesity is more a definition of having excessive body fat rather than having excessive body weight. Although body weight is an important health risk indicator, the amount of body fat, especially the abdominal fat, is more directly related to diseases. This is because lipids released from visceral fat could enter the portal vein and circulate to the liver resulting in higher total cholesterol and LDL cholesterol. Maintaining a healthy body fat percentage can reduce risk and help prevent the onset of these conditions. Because body weight does not reflect percentage of body fat mass and lean mass, a muscular, lean person could have a body mass index (BMI) over 30 (a criterion for being obese) even though he has a high amount of muscle mass and a low amount of body fat. Therefore, body composition is a much better indicator of overall health and fitness than body weight alone.



Conjugated linoleic acid (CLA) is a fatty acid produced by ruminants. It has effects on body weight by reducing body fat.

Body fat mass reduction

CLA's effect on body fat mass was first demonstrated almost a decade ago in mice, and research has since confirmed these findings to include several species, with some variation by animal type and CLA isomer. In addition to extensive animal data, over 20 well-designed clinical studies investigating different doses of the CLA-mix (50:50 c9,t11 and t10,c12) in over 1.200 human subjects for periods of 4 weeks to 2 years have been published. Many clinical studies have shown that CLA improves body composition with or without combination with exercise and in lean, overweight, and even obese subjects. One of the most important long-term studies demonstrated up to 10% reduction in body fat in overweight subjects following 1-year supplementation with CLA without additional exercise.[4] Another study on CLA supplementation among overweight adults partly performed during the holiday period confirmed the beneficial effects of CLA on body composition and showed a significant reduction of body fat mass.[5]

The totality of the evidence suggests a moderate body fat reduction by CLA mixture which was confirmed by a recent meta-analysis.[6] The meta-analysis collected and analyzed 18 eligible CLA studies that were longitudinal, randomized, double-blind, placebo-controlled human clinical trials using validated body composition measurements (dual-energy X-ray absorptiometry (DEXA), hydrodensitometry, skin-fold thickness, bioimpedence analysis (BIA), air-displacement plethysmography, total body water by ^{18}O isoptope dilution). The researchers concluded that among participants given 3.2 g/day, CLA produces a significant but modest reduction of fat mass of 0.09 kg a week compared to participants in the placebo group. This effect was observed in both short-term and long-term studies and in various subject populations. Furthermore, CLA may be most effective in reducing fat mass and increasing lean mass when combined with enhanced physical activity. In a study on 20 healthy, lean humans performing a standardized physical exercise program for 4.5 h per week, 12 weeks of CLA supplementation resulted in a significant 20% body fat reduction, while fat mass in placebo supplemented subjects remained unchanged.[7]

Overall, a recent study confirmed that CLA in foods is as effective as it is in supplement forms. Spanish researchers analyzed the effect of CLA fortified milk compared to conventional low fat milk in a group of healthy overweight subjects carrying about 60 minutes physical activity four times a week. Over a period of three months women reduced their body fat mass by 6% and men by 8%. These results suggest that CLA fortified milk combined with physical activity show superior benefits than exercising itself.[8] In summary, when the high-quality CLA-mixed isomers were used in well designed studies with adequate numbers of subjects, there was an indication of significant body fat mass reduction relative to placebo controls regardless of delivery vehicle.'

Mechanism for decreasing body fat mass

The exact mechanism through which CLA is able to decrease body fat mass is yet not clear. However, it does appear that CLA has two main sites of action: the adipocytes that are the principle site of fat storage, and the skeletal muscle cells that are the principle site of fat burning.[9] Studies have shown that CLA inhibits the activity of lipoprotein lipase (LPL) and stearoyl-CoA desaturase, and stimulates the breakdown of stored fat in the adipocytes (lipolysis).[10, 11, 12] LPL is the enzyme that transfers dietary fat after a meal into the adipocytes for storage. By inhibiting the LPL activities, CLA could reduce lipid uptake into adipocytes.[12] The t10,c12-CLA isomer may also affect the number of newly formed adipocytes by reducing preadipocyte differentiation,[13,14] or existing number of adipocytes by increasing adipocyte apoptosis or programmed cell death.[15,16] Other evidence demonstrated that carnitine palmitoyltransferase (CPT) activity is increased with CLA. The increased CPT activity in skeletal muscle cells enhances the rate of fatty acid transport into the mitochondria and results in an increased β-oxidation.[12] This may explain the enhancement of oxygen consumption and energy expenditure reported in CLA-fed OLETF rats[17] and more recently in human studies.[18]

CONJUGATED LINOLEIC ACID

In summary, it is likely that CLA decreases body fat mass through four possible actions:

1. Decreasing the amount of fat that is stored after eating (decreases LPL).
2. Increasing the rate of fat breakdown in fat cells (lipolysis) and the rate of fat burning in the mitochondria (CPT and β-oxidation).
3. Reducing proliferation and differentiation of preadipocytes to mature adipocytes.
4. Decreasing the total number of fat cells (apoptosis).

The mechanisms are supported mostly by data from animal studies and in vitro studies using cultured mouse adiposities, human adipocytes, and modified markers of differentiation as well as cultured human preadipocytes.[9]

Immune modulation – A new area of CLA research

A new area of CLA research is the area of immune modulation. There is emerging evidence that excess adipose tissue produces and secretes circulating factors, or 'inflammatory' mediators like TNF-α that may trigger a number of chronic conditions such as atherosclerosis, hypertension and dyslipidaemia. In obese subjects, levels of these mediators are significantly higher compared to non-obese.[19] After CLA supplementation, a reduction of TNF-α is observed in a number of intervention studies in overweight and obese subjects and this can be interpreted as a favourable modulation of the immune status into a more anti-inflammatory profile.[20] A reduction of plasma levels of inflammatory mediators could also be demonstrated in a CLA intervention study in adult subjects with birch pollen allergy. Individuals in the CLA group reported significantly less sneezing and a tendency towards fewer nasal symptoms.[21] These results confirm previous work by a research group in Canada who supplemented subjects with mild allergic asthma and found reduced airway hyperreactivity and airway inflammation.[22] The investigators concluded that CLA can attenuate the severity of asthma symptoms and could provide benefit in the relief of airway inflammation.

Furthermore, CLA supplementation could be particularly beneficial for immunocompromised individuals who are slow or low responders to vaccination, and CLA could have particular relevance for the elderly population incapable of mounting a sufficient response to confer immune protection.[23] Additional studies are needed to confirm CLA's immunomodulatory qualities.

Absorption and distribution

The metabolism of CLA has been widely studied and reported, and follows the standard pathway of dietary fats. Dietary fats enter the intestine in the form of triglycerides (TG) or free fatty acids (FFA). Ingested TGs are generally enzymatically broken down by pancreatic lipase in the small intestine into FFA, mono- or diglycerides. These are then incorporated into micelles for uptake into intestinal epithelial cells (enterocytes). Within these cells, the monoglycerides are reacylated, leading to the formation of new triglycerides. Reconstituted triglycerides, together with phospholipids,

cholesterol and apoproteins, are then assembled to form chylomicrons, which are released into the lymphatic system. The function of chylomicrons is to deliver dietary triacylglycerols to adipose and muscle tissue, and dietary cholesterol to the liver. In the capillaries of adipose tissue and muscle, fatty acids of the chylomicrons are removed from the triacylglycerols by the action of lipoprotein lipase, which is found on the surface of the endothelial cells of the capillaries. The FFA are then absorbed by the tissues, and are re-esterified into TG's and phospholipids for storage as a source of energy for the body or as structural components of cell membranes. Thus, chylomicrons are reduced in size by the removal of lipids. The resulting particle is a chylomicron remnant, which is taken up primarily by the liver via specific receptors and endocytosis.

Animal studies have shown that the absorption and distribution of different CLA isomers is very similar to that of linoleic acid.[24] Eighty percent of the absorbed dose of total CLA was carried in chylomicrons, the remaining 20% in very low density lipoproteins. Approximately 95% of total CLA absorbed was incorporated in triglycerides and 5% in phospholipids.[25] As human intervention studies have shown that CLA plasma levels correlate well with the CLA concentrations in supplemented food,[26] it is obvious that CLA isomers are also well-absorbed in the human body.

Metabolism

CLA is metabolized by two distinct pathways, so-called desaturation and oxidation. CLA is desaturated by two enzymes: Δ6 desaturase and Δ5 desaturase.[27,28] The metabolites produced depend upon the type of fatty acids present in the diet.[29] For example, when CLA is fed to rats deficient in linoleic and linolenic acid, the c9,t11 and c10,t12 CLA isomers are converted into conjugated isomers of arachidonic acid[30]. When rats were fed a fatty acid rich diet, the c9,t11 CLA isomer was converted into γ-linoleic acid with cis or trans configuration in positions 8, 11, 13 as the final end product.[31] The c10,t12- CLA isomer was converted into α-linoleic acid and into hexadecadienoic acid.[31] CLA metabolites are then incorporated into the lipid component(s) of adipose tissue, the liver, heart and kidney.[32]

Excretion

Animal studies have demonstrated that metabolites of CLA are extensively excreted from the body in expired air (up to 70% of the total dose of CLA was converted into CO2), and lesser amounts in urine and feces. The extent to which CLA metabolites were excreted in expired air was time-dependent, reaching a plateau after 12 hours.[33]

Food sources

Fats of ruminants are among the richest natural sources of CLA (Table 1). The amount of CLA present in dairy products varies according to animal breeding, animal age and the processing of the product, but the major determinant appears to be the feed. CLA concentration in milk, for instance, can be positively influenced by the diet of the animal. Supplementing the diet with polyunsaturated oils that contain either linoleic acid (corn oil or sunflower oil) or linolenic acid increases the CLA content of milk fat substantially.[34] The average CLA concentrations in cows' milk typically range from 2.5 to 17.7 mg of CLA/g milk fat.[35] Regarding meat from ruminants, the content of CLA ranges from 1.2 to 6.8 mg/g total fat in beef, which is comparable to the CLA content of lamb with values up to 5.6 mg CLA/g total fat.[34] The content of CLA in non-ruminant animals like fish and food products derived from fish is negligible in comparison to dairy products, ranging from 0.1 to 0.9 mg/g fat.[36]

CONJUGATED LINOLEIC ACID

Table 1: Dietary sources of CLA[34]

Food	Total CLA (mg/g fat)
MEAT & FISH	
Lamb	5.6
Fresh ground beef	4.3
Veal	2.7
Fresh ground turkey	2.5
Chicken	0.9
Pork	0.6
Salmon	0.3
CHEESE	
Ricotta	5.6
Mozzarella	4.9
Cottage cheese	4.5
Parmesan	3.0
DAIRY PRODUCTS	
Homogenized milk	5.5
Butter	4.7
Plain yoghurt	4.8
Egg yolk	0.6
VEGETABLE OIL	
Safflower	0.7
Sunflower	0.4
Peanut	0.2
Olive oil	0.2

Intake

The average daily intake of CLA is reported to be around 100-300 mg CLA/day worldwide (Table 2). The highest level reported (i.e. 1,000 mg/day) has been observed in a Hare Krishna community in Australia, due to high levels of ghee and butter consumption. Analyses of the CLA content in breast milk of these women revealed relatively high values, and were clearly related to the high intake of CLA-containing products.[37]

Table 2: Intake of CLA in Europe and United States

Estimated Intake of CLA in Humans from Background Diet (Europe and United States)[37]				
Nation	Subject	Method	CLA Intake (mg/day)	Ref.
Australia	Adults	NR	500-1000	36
U.S.	Adults	Diet Records	127	38
Germany	Adult males	FFQ	430	39
Finland	Adults, High Dairy	Diet Records	310	40
	Adults, Low Dairy	Diet Records	90	
Finland	Adult women	FFQ	132	41
Sweden	Males	Diet Records	160	42
Netherlands	Adults	Diet Records	200-400	43

NR = Not reported

Safety

The safety of CLA is supported by over 50 clinical human studies. Side effects are rare and related to the gastro-intestinal tract, similar to effects generally observed for fatty oils. CLA 50:50 isomer mix has been accepted by the US FDA as Generally Recognized as Safe (GRAS) up to a daily consumption of 3g.

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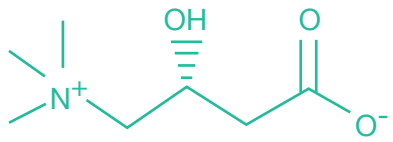
L-CARNITINE

Chemically, L-Carnitine, (gamma-trimethylamino-hydroxybutyric acid), is a small-molecular-weight polar molecule and a quaternary amine. L-Carnitine is naturally occurring in all mammalian species and is found in almost all cells.[1] The human pool of L-Carnitine is around 20 g with 98% of this within the cardiac and skeletal muscle pool, 1.4% in the liver and kidney, and 0.6% in extracellular fluid[2,3,4]. In 1905 L-Carnitine was isolated for the first time from muscle tissue. Its structure was established in 1927 (Figure 1).[5] Prof. Strack from the University of Leipzig in Germany published his first article about L-Carnitine in 1935[6] and initiated decades of investigations into the physiological functions of this substance. L-Carnitine was shown to be an essential nutrient for a meal worm (Tenebrio molitor) and was therefore called vitamin B_T.

Figure 1: Chemical structure of L-Carnitine



Introduction

By the 1960s the essential role of L-Carnitine in the utilization of long chain fatty acids for energy was confirmed, and the latest research has found that L-Carnitine can actually increase fatty acid oxidation in healthy adults (Figure 2).[7] Numerous clinical studies have reported upon the beneficial effects of L-Carnitine supplementation, and the number of publications per year on this substance is still increasing.[8]

Importance for health

Extensive clinical research has discovered that L-Carnitine has a beneficial role to play in a broad array of applications.

Exercise

Studies in athletes have shown that L-Carnitine supplementation may foster exercise performance.[9] Both an increase in maximal oxygen consumption and a lowering of the respiratory quotient indicate that L-Carnitine has the potential to stimulate lipid metabolism.

Supplementation with L-Carnitine prior to high intensity exercise was found to be significantly effective in assisting recovery both in young and in old subjects.[10,11] The researchers observed a decrease in the production of free radicals, less tissue damage and reduced muscle soreness after exercise and a better utilization of fat as an energy source during recovery. This effect increased in response to the daily dosage of L-Carnitine, with statistical significance already shown at a dosage of 1 g L-Carnitine per day.[12] Supplementation with L-Carnitine induces an increase in muscle oxygen consumption, providing a potential mechanism for reduced hypoxic stress following resistance exercise.[13]

Fatty acid oxidation

Studies also indicate that L-Carnitine is useful as part of a weight management program when combined with exercise and calorie restriction.[14,15,16] It has been shown by two different research groups that oral supplementation of L-Carnitine stimulates in vivo long chain fatty acid metabolism in healthy adults. Prior to, and after ten days of L-Carnitine supplementation, the subjects received labelled fatty acids with a meal. Labelled CO_2 as the breakdown product of the labelled fatty acids was then measured in the exhaled air. In the group that received L-Carnitine, a significant increase in exhalation of labelled CO_2 was observed, indicating a significant increase in fatty acid oxidation.[17,18]

L-Carnitine occurs naturally in all mammalian species and is found in almost all cells. Studies in athletes have shown that L-Carnitine supplementation may foster exercise performance.

Cardiovascular health

Clinical data indicates that L-Carnitine supplementation can positively support healthy heart muscle[19], can significantly increase heart muscle viability[20] and is beneficial in supporting a healthy heartbeat.[21] L-Carnitine supplements have a favourable effect on blood lipid levels, and are demonstrated to be helpful for people with angina, arrhythmias and heart failure.[22,23]

Infants

In addition, L-Carnitine is considered to be an essential nutrient for infants because, unlike adults, infants are unable to synthesize sufficient L-Carnitine in their bodies to meet their requirements.[24] L-Carnitine is present in breast milk and for many years now, manufacturers of soy-based infant formula have been fortifying their products with L-Carnitine, which would otherwise be devoid of this conditionally essential nutrient.[25]

Vegetarians

As the intake of dietary L-Carnitine is directly linked to meat intake, and meat is the richest source of this nutrient, vegetarians and anybody who reduces his meat intake gets very little L-Carnitine with the diet. If L-Carnitine intake is low, however, the body has to rely almost entirely on endogenous synthesis to meet its needs. A vegetarian diet, however, is frequently also low in some of the nutrients that are essential for L-Carnitine biosynthesis in the body.[26] Indeed, humans following a lacto-ovo or a strict vegetarian diet over years have been shown to have decreased plasma L-Carnitine concentrations and may benefit from supplementary L-Carnitine[27].

Male fertility

High concentrations of L-Carnitine and its metabolite acetyl-L-Carnitine are found in sperm,[28] and both have a crucial role to play in sperm energy metabolism. The concentration of L-Carnitine in semen is closely linked to sperm quality.[29] Clinical studies suggest that L-Carnitine supplementation over a period of 3 to 6 months can positively affect sperm concentration, sperm count, percentage of motile sperm and the percentage of sperm with rapid progression.[30,31,32,33,34,35]

Healthy aging

Various studies in elderly subjects show improved mental status and learning ability, improved immune function or an increase in muscle mass after supplementation with L-Carnitine.[36,37,38] Thus, L-Carnitine can be regarded as the ideal nutrient for a long life, as it comprises all the benefits that seniors need to stay fit and healthy in both mind and body.

L-CARNITINE

Food sources

Endogenous synthesis

L-Carnitine is supplied to the body through both endogenous synthesis and food intake. The human body synthesizes about 20 mg of L-Carnitine every day. The major sites of L-Carnitine biosynthesis are the liver and kidneys. This process requires two essential amino acids, protein-bound lysine and methionine, plus vitamin C, iron, vitamin B_6 and niacin, and involves a series of enzymatically catalyzed reactions.[39] The requirement for all these essential nutrients implies that malnutrition has a highly negative impact on L-Carnitine biosynthesis.

Sources

For the most part, however, the daily L-Carnitine requirement is met by food intake. Products of animal origin contain reasonable amounts of this nutrient, whereas foods of plant origin contain only very few, if any, L-Carnitine (Table 1).

Table 1: L-Carnitine content in selected foods [mg/100g]

Food of animal origin (uncooked)	L-Carnitine [mg/100g]	Food of plant origin (uncooked)	L-Carnitine [mg/100g]
Lamb	190	Mushroom	2.6
Beef	143	Carrot	0.4
Pork	25	Bread	0.4
Poultry	13	Rice	0.3
Fish	3-10	Banana	0.1
Egg	0.8	Tomato	0.1

Absorption and metabolism

A variety of test systems including animals, animal intestinal preparations, human intestinal biopsy samples and human intestinal epithelial cell lines have found that the uptake of L-Carnitine into the intestinal epithelium of the small intestine occurs partly via carrier-mediated transport and partly via passive diffusion.[40,41,42] Uptake in the colon appears to be restricted to a passive component only.[43] Therefore the small intestine can be considered as main site for L-Carnitine absorption. The absorption of L-Carnitine is characterized by slow mucosal uptake, prolonged mucosal retention and slow mucosal exit into the blood. Therefore, in humans the time to achieve maximum plasma concentrations after oral administration of L-Carnitine can be up to 4-6h, or longer.[44] Absorbed L-Carnitine is already acetylated in the intestinal cells; a mixture of Acetyl-L-Carnitine and L-Carnitine is then delivered to the liver via the portal vein or released directly into the systemic circulation.[44] In mammals, L-Carnitine is always present as a mixture of free and acylated L-Carnitine. Typically, in healthy humans, approximately 80-85% of L-Carnitine exists as the free form in the plasma. The L-Carnitine plasma levels are regulated mainly by the kidneys, and are age- and sex-dependent.

Intake

A well-balanced, non-vegetarian Western diet is estimated to provide 100-300 mg of L-Carnitine each day.[45] In Europe, however, dietary L-Carnitine intake has decreased by about 20% over the last decade, mainly as a result of a decrease in beef consumption.

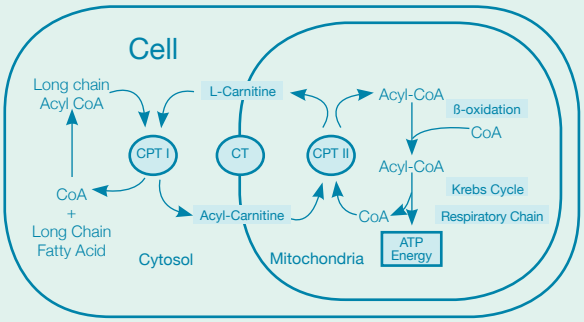
Table 2: Average dietary L-Carnitine intake in various countries [mg/day]

Country	mg L-Carnitine/day
Mongolia	425
Australia	301
US	236
Europe	129
Japan	75
India	24

Recommended intakes

No dietary reference intakes (DRIs) or recommended daily allowances (RDAs) have yet been set for L-Carnitine, because such values exist only for vitamins and minerals and other essential substances. L-Carnitine is regarded as a conditionally essential nutrient as under certain situations the needs may exceed the capacity for endogenous synthesis.

Figure 2: Metabolic pathway of L-Carnitine in the cell



Safety

L-Carnitine has a host of applications, ranging from approved pharmaceutical indications and nutritional supplementation to animal feed formulations. The EFSA (European Food Safety Authority) has made an extensive safety evaluation and concluded that up to 2 g L-Carnitine or the equivalent 3g L-Carnitine L-tartrate are regarded as safe for daily consumption.[46]

In contrast, D-Carnitine, as pure substance[46] or in the form of racemic DL-Carnitine, has been found to be not only physiologically inactive but also inhibits the uptake and functions of the natural isomer L-Carnitine,[45, 47, 48] which can then lead to a functionally relevant depletion of L-Carnitine in skeletal and cardiac muscle.[49] Serious side effects to animal as well as human health have been observed with applications of racemic DL-Carnitine.[50, 51, 52, 53, 54, 55] Results of experimentation with racemic DL-Carnitine, and subsequently also with the pure isomers D-carnitine and L-Carnitine have been reviewed by Borum and Fisher[56] and also by Meier.[57] The US FDA has long maintained that D-Carnitine and DL-Carnitine are not generally recognized as safe and are, therefore, illegal food additives.

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COENZYME Q10

Coenzyme Q10 (CoQ10) was first isolated from bovine heart mitochondria in 1957, and its chemical structure was identified in 1958. It is also known as ubiquinone (ubiquitously occurring quinone) because of its widespread presence in living organisms. In healthy individuals CoQ10 can be biosynthesised to a certain degree.

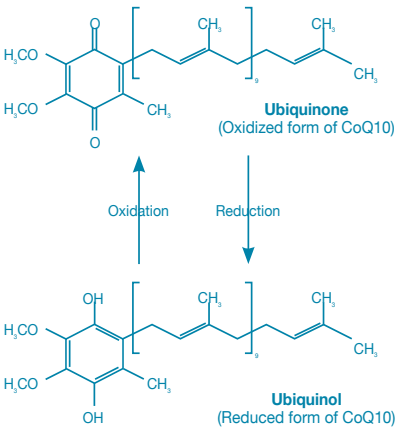
Introduction

Coenzyme Q10 is a liposoluble vitamin-like substance and has 10 isoprene units. It exists in nature and in the body in two forms: the oxidized form, called ubiquinone, and the reduced form which is named ubiquinol (Figure 1).

CoQ10 is an essential carrier for the electron transfer in the mitochondrial respiratory chain for the synthesis of adenosine triphosphate (ATP), and its reduced form (ubiquinol) acts as an important antioxidant in the body. Through these functions, CoQ10 supplementation has beneficial effects in humans for the maintenance of good health.[1,2,3]

CoQ10 is an integral and essential part in all human cells and is the only endogenously synthesized lipid soluble antioxidant. Ubiquinol, the reduced form of CoQ10, has recently become available in stable form.

Figure 1. Chemical structure of CoQ10



Importance for health

Energy production

It is well established that CoQ10 is essential for cellular energy conversion and ATP production in all cells of the body. Therefore it plays a crucial physiological role in maintaining good health. ATP is a high energy phosphate substance necessary to fuel all cellular functions. The major part of ATP production occurs in the inner membrane of mitochondria, where CoQ10 is located as a vital electron and proton carrier in the mitochondrial electron transport. CoQ10 supports ATP synthesis in the mitochondrial inner membrane and stabilises cell membranes, thus preserving cellular integrity and function.[3,4,5]

Energy and sporting activity: CoQ10 is reported to be effective in sporting activity by improving the physical work capacity (especially, in aerobic exercise) through activation of energy supply and favourable effects on lipid metabolism, and also through its anti-oxidative muscle-protective action.

Antioxidant function

It is well established that CoQ10 acts in its reduced form (ubiquinol) as an antioxidant. Ubiquinol represents more than 93 - 99% of the total CoQ10 pool in human plasma and is an important antioxidant in plasma lipoproteins.[6,7,8,9,10] Ubiquinol inhibits protein and lipid oxidation in cellmembranes, and it prevents the initiation of lipid peroxidation, oxidative injury to DNA and other molecules.[3,5,11]

CoQ10 acts as an antioxidant through several mechanisms which essentially fall into two categories: direct reaction with free radicals and regeneration of the active form of vitamin E by reducing the alpha-tocopheryl radical.[12,13]

Peroxidation of plasma lipoproteins, namely LDL, is known to play an important role in the formation of foam cells and in the development of the atherosclerotic process. Studies in the last decade have demonstrated that the content of CoQ10 in human LDL affords some protection against the oxidative modifications of LDL particles, thereby lowering their atherogenic potency.[14,15,16] Studies on isolated serum lipoproteins demonstrate that CoQ10 is the most reactive antioxidant in these particles and protects them from oxidative damage.

Antioxidant and anti-aging: The aging process is fundamentally influenced by CoQ10. The mitochondrial respiratory chain is a powerful source of reactive oxygen species, which are considered to play a major part in the deterioration of cell structures accompanying aging. As CoQ10 is an integral part of the respiratory chain and thereby located exactly where the free radicals are generated, its antioxidant properties are very important for the overall anti-oxidative capacity of the mitochondria.[17] The ubiquinol ratio is a potential biomarker of the aging process and ratio of Ubiquinol/LDL-C is likely to be a risk factor for atherogenesis.[10,18] German researchers suggested that the ubiquinol-ratio in human plasma may represent a sensitive index of oxidative stress in vivo especially indicative of early oxidative damage.[19]



Coenzyme Q10 is an essential carrier for the electron transfer in the mitochondrial respiratory chain for the synthesis of ATP, and its reduced form (ubiquinol) acts as an important antioxidant in the body.

Heart and cardiovascular health

Coenzyme Q10 helps to maintain a healthy cardiovascular system. There is evidence of CoQ10 deficiency in hypertension, heart failure and in statin-treated hypercholesterolemic individuals.

Blood pressure: Blood pressure is a well-established biomarker for heart health. A meta-analysis of 12 clinical trials of CoQ10 for hypertension has shown that CoQ10 is effective in lowering systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg without significant adverse events.[20]

Heart function: There is substantial evidence that heart function is improved by the supplementation of CoQ10.[21,22] A meta-analysis of the use of CoQ10 (60-200 mg/day) in randomised clinical trials in people with congestive heart failure showed a significant and clinically relevant improvement in various parameters of heart function.[23] A comprehensive review of the use of CoQ10 (50-200 mg/day for 1-12 months) in cardiovascular indications showed that the adjuvant supplementation with CoQ10 in people with chronic heart failure should be recommended.[24]

CoQ10 plasma concentrations have been demonstrated as an independent predictor of mortality in chronic heart failure.[25] Ubiquinol dramatically improves absorption in patients with severe heart failure and is correlated with both clinical improvement and improvement in measurement of left ventricular function.[26]

Statins: Statins (HMG CoA reductase inhibitors; cholesterol lowering drugs) may decrease body CoQ10 levels below the threshold that is required for numerous cellular processes. The depletion of CoQ10 is dose related and could be particularly important in the elderly where CoQ10 levels are generally low, but also in those with pre-existing heart failure. Statin-induced CoQ10 deficiency is completely preventable with supplemental CoQ10, with no adverse impact on the cholesterol lowering or the anti-inflammatory properties of the statin drugs.[27]

LDL: Ubiquinol supplementation in humans mediates distinct reducing effects on LDL cholesterol levels (-12.7%) with a pronounced effect on atherogenic small dense LDL particles.[28]

Food sources

Coenzyme Q10 is present in a variety of foods. The examples are shown in Table 1. The higher levels of CoQ10 are found in meats and fish. Vegetables and dairy products contain relatively low levels.

Table 1. CoQ10 content in foods

Food	CoQ10 content (µg/100g wet weight)			
	Kamei (1986)[29]	Weber (1997)[30]	Mattila (2001)[31]	Kubo (2008)[32]
Beef	3100	3100	3650	3030-4010
Chicken	2100	1700	1400	1710-2500
Fish	550-6430	430-2700	850-1590	180-13000
Broccoli	860	660	–*	701
Potato	100	52	50	105
Milk	40	–*	10	31
Egg	370	150	120	73

*not determined

Absorption and metabolism

Exogenous CoQ10 is absorbed from the small intestinal tract. It is best absorbed if it is taken with a meal. When single oral doses of CoQ10 at 300 mg were given with and without breakfast to 5 volunteers, the serum concentration of CoQ10 for non-fasting subjects was clearly higher than that for fasting subjects. These results indicate that food greatly enhances the absorption of CoQ10.[33]

CoQ10 is predominantly excreted into feces, and it is also excreted via the bile duct. About 62.5% of the orally administered CoQ10 was recovered in the feces during multiple dosing (2 days at 333 mg/day and 5 days at 100 mg/day) in healthy male subjects.[34]

COENZYME Q10

Intake

The average daily intake of CoQ10 from food is estimated to be around 10 mg. According to Weber, the average CoQ10 intake of the Danish population was estimated at 3-5 mg/day, primarily derived from meat and poultry.[35] However, using the same food consumption data for the Danish population used by Weber[35] and CoQ10 content data obtained by Kamei[29], average CoQ10 intake was estimated to be 4 to 21 mg/day (Table 2). Hallström estimated that the average CoQ10 intake of the Swedish population was between 2 mg/day and 20 mg/day.[36] Ubiquinol accounts for 46% of the total coenzyme Q10 intake in Japanese daily food consumption.[32]

Table 2. The Dietary intake of CoQ10 in the Danish population estimated by using the CoQ10 content data obtained from Kamei et al.[29]

Food group	CoQ10 content (µg/g wet)*1	Intake of food (g/day)*2	CoQ10 intake (mg/day)
Meat (pork, chicken, beef)	31.0 (21.0 – 41.1)	120	3.72 (2.52 – 4.93)
Fish (7 different samples)	27.1 (5.5 – 64.3)	26	0.70 (0.14 – 1.67)
Cereals (5 different samples)	2.3 (0.6 – 4.9)	227	0.52 (0.14 – 1.11)
Vegetables (16 different samples)	3.9 (1.0 – 10.2)	270	1.03 (0.27 – 2.75)
Fruit (3 different samples)	1.26 (0.49 – 2.2) (Weber et al.)*30	154	0.19 (0.08 – 0.34)
Dairy products (butter, cheese, cow milk)	3.2 (0.4 – 7.1)	426	1.36 (0.17 – 3.02)
Egg (chicken egg)	3.7	36	0.13
Dietary fat	27.8 (4.0–92.3)	79	2.20 (0.30 – 7.29)
Total ingested per day		1338	9.85 (3.75 – 21.24)

*1 Data are from Kamei et al. (1986)[29] except fruit; values are the mean value of determinations, and values in parentheses indicate low value – high value in the samples

*2 Daily intake of food in Denmark (from a National dietary survey, 1986), cited from Weber et al. (1997)[30]

*3 Data are from Weber et al. (1997)[30]

Food supplements and food fortification

The body's pool of CoQ10 is derived from 3 sources, namely, endogenous synthesis, food intake and oral supplements. The mean plasma level of normal individuals is about 0.8 µg/ml.[37]

CoQ10 deficiency may result from decreased dietary intake of CoQ10, impairment in CoQ10 biosynthesis, increased utilisation of CoQ10 by the body (oxidative stress) or any combination of these factors. Additionally, tissue levels of CoQ10 decrease with aging.[38]

For people low in CoQ10 levels, endogenously synthesised CoQ10 is not sufficient for the maintenance of good health, and additional intake must come from fortified foods or food supplements. Nutritional replenishment requires supplementation with higher levels of CoQ10 than those available in most foods. It has been shown that 100 mg/day CoQ10 is needed to get CoQ10 into deficient tissues. This cannot be achieved from the normal diet.

The Physician Desk Reference (PDR) for nutritional supplements in the USA indicates that daily doses of CoQ10 range from 5 to 300 mg in different formulations such as oil-based capsules, powder-filled capsules and tablets.[39]

There are 3 methods used for the manufacturing of CoQ10: yeast fermentation, bacteria fermentation and chemical synthesis. The yeast fermentation process results in CoQ10 with the so-called "all-trans configuration", which means that it is identical to naturally occurring CoQ10 found in meat, fish and other products. CoQ10 produced by chemical synthesis also generates the cis-isomer (a configuration of the molecular structure not found in naturally occurring CoQ10). The safety of yeast fermentation CoQ10 has been confirmed by various safety studies.

Recommended intakes

No dietary reference intakes (DRIs) or recommended dietary allowances (RDAs) have yet been set for CoQ10.

Safety

After more than 30 years' use in humans and many clinical studies with CoQ10, there are no reports of serious adverse effects associated with daily supplements of CoQ10.

In a 52-week oral gavage chronic toxicity study in rats it was concluded that even the high-dose of CoQ10, 1,200 mg/kg/day for 52 weeks, was well tolerated by male and female rats and the NOAEL of CoQ10 could be estimated to be 1,200 mg/kg/day.[40] This results in an acceptable daily intake (ADI) of 12 mg/kg/day calculated from the NOAEL by applying a safety factor of 100, i.e. 720 mg/person/day for a 60 kg person.

The safety assessment of CoQ10 in healthy adults (n=88) was assessed in double-blind, randomized, placebo-controlled trials at high dose supplementation of 300, 600 and 900 mg for 4 weeks and concluded to be well-tolerated and safe for healthy subjects at intakes of up to 900 mg/day.[41]

On the basis of a large number of published data from clinical studies with CoQ10, a risk assessment for CoQ10 was performed according to the safety evaluation method from the Council for Responsible Nutrition (CRN). The results indicate that a NOAEL cannot be set because no adverse effect causally related to CoQ10 in humans could be found, and therefore, the observed safety level (OSL) for CoQ10 was identified as 1,200 mg/day.[42,43]

Australian authorities (TGA) have notified that a maximum daily recommended dosage of CoQ10 is 150 mg.[44]

The Japan Health Food & Nutrition Food Association has proposed that the maximum daily intake of CoQ10 is 300 mg/day.[45]

A Belgian ministerial order determined CoQ10 was safe for use in food supplements at 200 mg per day.[46]

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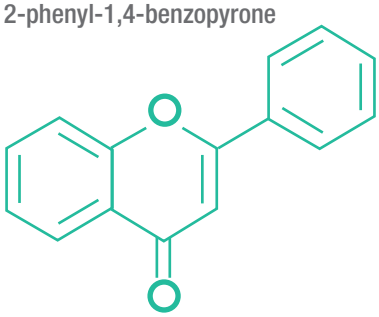
EPIGALLOCATECHIN GALLATE

Epigallocatechin gallate (EGCG) is the most abundant catechin found in green tea. Catechins belong to the family of flavan-3-ols that have a similar structure as flavonoids, but without the carbonyl group. Flavonoids are plant derived colored phenolic compounds with 2-phenyl-1,4-benzopyrone as a common backbone (Figure 1) that can be subdivided into the following subclasses: anthocyanidins, anthocyanins, flavanols (e.g. EGCG), flavanones, flavonols, flavones and isoflavones.[1] Over 3000 different flavonoids have been isolated from plant extracts. They are the major sources of red, blue and yellow pigments. Most naturally occurring flavonoids re present as glycosides.

Figure 1: 2-phenyl-1,4-benzopyrone



Introduction

In 1936 A. Szent-Gyorgi and his co-workers named flavones vitamin P since he found synergistic properties to vitamin C.[2] Although flavonoids exhibit biological activities, a deficiency sign could not be described that would prove the essentiality for humans. Therefore, the Joint Committee on Biochemical Nomenclature of the American Society of Biological Chemistry and the American Institute of Nutrition recommended replacing the term 'vitamin P' by bioflavonoids.[3]

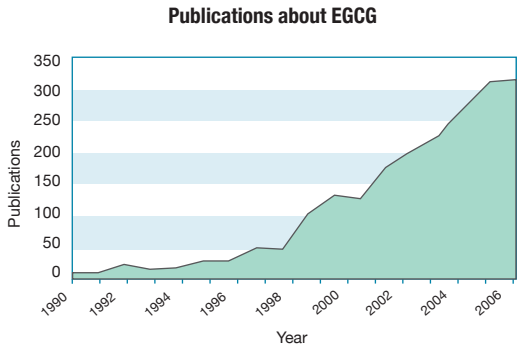
A mixed diet may provide over 1 g of flavonoids from fruits and vegetables per day. Epigallocatechin gallate (EGCG) is the major polyphenolic compound found in green tea Camellia sinensis. According to the USDA database for the flavonoids content of selected foods 100 g dry green tea leaves contain between 1.6 and 20.3 g of EGCG (mean 8.3g/100 g).[5] Catechin and epicatechin are epimers and epigallocatechin (EGC) contains an additional hydroxyl group; EGCG is the gallic acid ester of EGC.

Although green tea has been known for decades for its health sustaining benefits, the scientific community focused its interest on the active ingredients only a few years ago. A true turn-around of research activities about EGCG could be observed during the millennium change into the 21st century. Figure 2 shows the number of publications about EGCG between 1990 and 2007 indicating the growing attention for this compound during the past years.

In vitro studies, animal experiments and human trials demonstrate multiple interventions of EGCG with metabolic processes that improve the control for a normal performance of the organism.

Thus, an adequate intake of EGCG, an antioxidant by nature, has been discussed to exhibit a positive influence in the field of cardiovascular health, obesity, blood glucose control, oral health, immunological processes, and even cancer development.

Figure 2: Number of publications about EGCG[6]



Although data collected from observational studies are usually based on tea consumption and intervention trials often compare a green tea extract with a placebo, EGCG is considered to be the most active ingredient of green tea.

Importance for health

Obesity

Obesity is a major risk factor for a number of disorders such as diabetes, hypertension and heart disease. Usually the number of fat cells and their lipids are regulated by complex interactions of external and internal factors that should prevent the development of obesity. A reduction of overweight can be achieved either by increasing the energy expenditure or by reducing the energy consumption. Physical exercise is the method of choice to use up excessive energy stores. Alternatively, thermogenesis might be stimulated in order to increase the resting metabolic rate.

Ten volunteers spending 24 hours in a respiratory chamber during a placebo controlled cross-over study had a significantly lower respiratory quotient (RQ) when they received 270 mg EGCG in the form of a green tea extract compared to placebo or 150 mg caffeine.[6]

A lower RQ indicates a switch towards fat as an energy source. ECGC may modify the signaling cascade that regulates the proliferation and differentiation of adipocytes. In addition, lipogenic enzymes are inhibited resulting in a reduced synthesis of fatty acid and triglycerides.[7] Thus, stimulating thermogenesis and fat oxidation gives EGCG the potential to modify body weight and body composition.

A mixed diet may provide over 1 g of flavonoids from fruits and vegetables per day. Epigallocatechin gallate (EGCG) is the major polyphenolic compound found in green tea Camellia sinensis.

Heart and cardiovascular health

EGCG is a powerful antioxidant and may inhibit inflammatory mediators. Therefore, EGCG may play an important role in reducing the risk of cardiovascular diseases where oxidative stress and pro-inflammatory processes are the principal causes.[8] In a placebo controlled cross-over study 42 volunteers received either 300 mg EGCG or placebo. The brachial artery flow-mediated dilation increased significantly 2 hours after the initial dose. The changes in vascular function paralleled plasma EGCG concentrations, which increased from 0.005 ± 0.02 µmol/L to 0.20 ± 0.17 µmol/L after acute EGCG. Thus, the improvement of endothelial function may account for the benefit of EGCG on heart health.[9] In addition, EGCG modestly reduced the diastolic blood pressure in a placebo controlled trial that may also contribute to the cardiovascular benefits of EGCG.[10]

Glucose control

A number of observational studies point at a beneficial interference between green tea consumption and glucose homoeostasis. In a double-blind, placebo controlled trial 38 overweight or obese postmenopausal women received either 150 mg EGCG or a placebo twice daily for 12 weeks. EGCG significantly decreased resting heart rate ($p < 0.01$) and reduced plasma glucose in subjects with impaired glucose tolerance ($p < 0.05$).[11] In a rodent model of diabetes mellitus type 2 EGCG improved oral glucose tolerance and blood glucose in food-deprived rats in a dose-dependent manner. In addition, the glucose-stimulated insulin secretion was enhanced.[12] Based on intervention studies with tea, a dose of 100 – 300 mg EGCG/day might be adequate to support glucose homeostasis.[13]

Oral health

Polyphenolic compounds isolated from Camellia sinensis, especially EGCG, inhibit the growth and adherence of Porphyromonas gingivalis onto the buccal epithelial cells at concentrations of 250-500 µg/ml.[14] Proteinases of P. gingivalis are implicated in certain forms of periodontal disease[15] that are inhibited by catechins like EGCG.[16]

Thus, EGCG may have the potential to reduce periodontal breakdown triggered by P. gingivalis. EGCG has also been shown to be effective in reducing acid production in dental plaque and mutans streptococci[17], which suggests that EGCG may be useful to prevent dental caries in humans.

Skin health

Skin has the largest epithelial surface of all organs. EGCG has been shown to have potential to protect the skin through various mechanisms. These include UV protection, antioxidant properties, anti-inflammatory effects, acceleration of keratinocyte differentiation, and anti-cancerogenic properties.[18] Most of the molecular mechanisms have been demonstrated by in vitro models and in animal trials. Evidence in humans is lacking but the promising animal data warrants further research.

Cancer

EGCG interferes with signaling pathways at several locations that are critical for cancerogenesis. Even though human data is not utterly compelling, tea constituents may still be used for the prevention of cancer at selected organ sites if sufficient concentrations of the agent can be delivered to these organs.[19]

The mechanisms of action have extensively been investigated, studies in cell lines led to the proposal of many mechanisms on the action of EGCG. Thus EGCG inhibits the dihydrofolate reductase (DHFR) from various sources such as chicken liver, bovine liver and E. coli[20] at concentrations that can be found in the serum and tissues of green tea drinkers.[21] Thus, it inhibits the DNA synthesis similar to methotrexate, an antifolate drug used in chemotherapy, but of course not as powerful and without side effects. Additionally, EGCG induces apoptosis in cancerous cells by inhibiting the activity of fatty acid synthase (FAS) that is over expressed in several types of human cancer cells such as prostate, breast, ovary, endometrium, lung and colon.[22]

During the early phase of growth a tumor lives on diffusion of nutrients and oxygen until a size of about 0.5 mm in diameter. Thereafter, the cancer initiates angiogenesis in order to have access to the circulating supply of nutrients. Furthermore, invasive tumors express proteases that degrade the extracellular matrix for the penetration of tissues and organs. EGCG interferes at different locations during the blood vessel formation and inhibits 2 types of proteases in vitro. EGCG may thus limit tumor growth and the formation of metastasis.[23]

EPIGALLOCATECHIN GALLATE

Food sources

Green tea is the major dietary source of EGCG.

EGCG content of dried tea leaves[4]

Tea	Content [mean (min. max)]; mg/g
Green Tea	83 (16, 203); n=60
Black Tea	36 (7, 71); n=15
Black Tea	12 (1, 51); n=69

The EGCG content of brewed tea depends on the quantity of tea leaves used, but according to this table one cup of green tea prepared with 1.5 g of tea leaves may contain around 100 mg EGCG.[4]

Intake

The intake of EGCG is substantial in countries with a high intake of tea like Japan where the average daily intake of EGCG varies between 120 - 383 mg for men, and 107 - 339 mg for women.[24] The estimated intake of EGCG in some European countries reflects the respective tradition of tea drinking.[25]

Country	Intake (mg/day)
Denmark	45
Holland	50

Recommended intakes

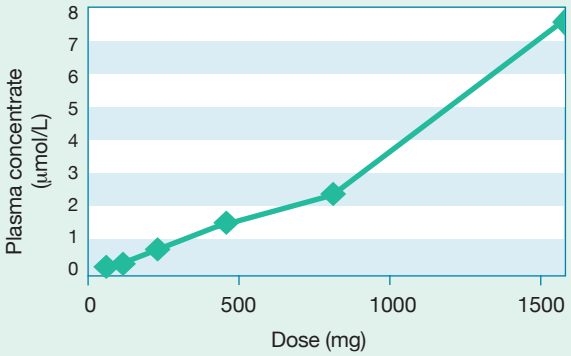
No Dietary Reference Intake for EGCG has been established. However, the evidence from various studies and in vitro experiments is strong enough to warrant a recommendation of a regular intake of EGCG. So far, an uptake between 100 to 200 mg per day can be recommended from efficacy and tolerability studies.

Absorption and metabolism

Orally administered EGCG is rapidly absorbed from the gut. The plasma levels increase almost linearly after a single oral dose of 50 to 1600 mg, followed by a multiphase decrease consisting of a distribution phase and an elimination phase. The peak level is reached 1.3 – 2.2 h after the ingestion.[26]

Three different metabolic pathways have been observed for EGCG in vitro systems including human liver microsomes, human placental cytosol, human jejunal cytosol, human saliva: methylation, glucuronidation and sulfation.[27] Over twenty metabolites have been found from EGCG. In addition, bacteria from the gut microflora are able to breakdown EGCG to simple compounds.

Plasma kinetics of EGCG after a single dose:



Safety

EGCG is predominantly found in the tea plant Camellia sinensis, with green tea being the main source. EGCG is the most abundant catechin in green tea and represents 25% to 40% of the total catechin content. Epidemiological studies show that a significant number of Asian people regularly drink several cups of green tea per day reflecting a long history of safe use. Further support of its safe use is provided by a number of clinical studies using green tea, green tea extract or pure EGCG. Single doses up to 1600 mg EGCG or repeated doses up to 800 mg EGCG daily were well tolerated and no signs of liver damage or any other clinically relevant adverse event were reported. The intake of EGCG had no effect on plasma concentrations of vitamins A, C, E and β-carotene.[28]

EGCG slightly inhibits the absorption of non-haem iron at a dose of 300 mg by 27% compared to placebo, which is less than reported from e.g. black tea.[29] Long-term consumption of 300 mg EGCG daily, divided in 150 mg EGCG with breakfast and 150 mg EGCG with dinner did not cause adverse events.[30] This set of data supports the history of safe use of EGCG under the above mentioned conditions. Nonetheless it should be noted that in 2008 the US Pharmacopeia published a review article about the safety of green tea extracts.[31] The article summarizes a number of reported liver adverse events.[30] The article did not differentiate between the processing of the different extracts, therefore the relationship of EGCG to different green tea extraction processes has not been established. The USP review recommended to make a cautionary statement as to persons with liver disorders on powdered green tea extracts.

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