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# Active components in food supplements

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# Abstract

The growing food supplement market, where supplements are both more diverse and more easily available (e.g. through Internet) formed the backdrop to the inventory of the active components in food supplements.The safety of an increased intake of food components via supplements was also at issue here. The inventory gives the minimum requirement, recommended daily allowance, toxic dose, observed dose in supplements, dietary source, physiological function and deficiency symptoms for each component. A distinction is made between water- and fat-soluble vitamins, major minerals, trace elements, hormones, fatty acids and associated nutritional factors. Of these components, a chronic high intake of the vitamins A, D, folate, calcium, iron, zinc and selenium in healthy persons can lead to adverse or toxic health effects. Special risk groups or risks for a high iron intake in combination with vitamin C, vitamin E, calcium and ß-carotene could be identified. The safety levels of the hormones, dehydroepiandrosterone and melatonin, have yet to be determined, they have been reported to be responsible for adverse side-effects.

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# Samenvatting

In dit rapport is een inventarisatie gemaakt van de actieve componenten die aanwezig zijn in voedingssupplementen. Van elke component is het volgende weergegeven: minimum behoefte, aanbevolen dagelijkse hoeveelheid (ADH), toxische dosis, waargenomen hoeveelheid in supplementen, bronnen en functie van de component en symptomen die optreden bij deficiëntie. De veel voorkomende stoffen in voedingssupplementen zijn onderverdeeld in de volgende categorieëen: water- en vet-oplosbare vitamines, mineralen, spoorelementen, hormonen, vetzuren en aanverwante voedingsfactoren.

De actieve voedingscomponenten kunnen onderverdeeld worden in twee globale categorieën: componenten die veilig zijn bij een inname van minstens 50 keer de ADH en waarvan verondersteld wordt dat geen toxische effecten optreden bij normaal gebruik en in de tweede categorie vallen stoffen die een veilige marge hebben van minder dan 50 keer de ADH en waarvan redelijkerwijs mag worden aangenomen of verwacht dat ze bij overdosering of bij risico-groepen negatieve effecten op de gezondheid veroorzaken. De volgende componenten behoren tot de laatste categorie: van de wateroplosbare vitamines is een hoge vitamine C inname mogelijk schadelijk bij mensen met een verstoord ijzermetabolisme (bijv. hemochromatose). Een hoge folaat inname kan het bestaan van een vitamine $B_{12}$-deficiëntie maskeren.
Van de vetoplosbare vitamines zijn vitamine A en D schadelijk bij een relatief lage inname. Een inname van vitamine A van ongeveer acht keer de ADH kan bij zwangere vrouwen afwijkingen aan de vrucht veroorzaken. Kinderen lijken ook erg gevoelig te zijn voor hypervitaminose D. Een hoge inname van vitamine E kan interfereren met de bloedstolling en is daarom bij patiënten met anti-stollingstherapie af te raden. Voor wat betreft de mineralen, zou de inname van zink beperkt moeten blijven tot twee tot vier keer de ADH. Een hoge calcium inname (> 2 keer de ADH) kan gastro-intestinale stress veroorzaken. Verder heeft selenium een bijzonder lage veilige marge van inneming. Van de aanverwante nutritionele factoren staat ß-caroteen in de belangstelling vanwege het toegenomen risico op longkanker in rokers na chronische consumptie van ß-caroteen van minstens tien keer de ADH vergeleken met de controlegroep.
Het verhogen van de inname van een specifieke component kan de opname van of interactie met andere componenten wijzigen en zo een onbalans creëren. Een voorbeeld hiervan is een mogelijke afname in de ijzerabsorptie wanneer specifieke calcium-supplementen worden ingenomen, waardoor personen met een marginale ijzerstatus een ijzerdeficiëntie ontwikkelen. Een ander willekeurig voorbeeld is dat, na een verhoogde chronische zink inname, een koperdeficiëntie ontstaat doordat zink het koper in enzymen vervangt.

# Summary

This report documents an inventory of the active components present in food supplements. Information on the minimum requirement, recommended daily allowance (RDA), toxic dose, observed dose in supplements, dietary sources, and the physiological function of the component and deficiency symptoms are given for each component. Substances frequently found in supplements like water- and fat soluble vitamins, major minerals, trace elements, hormones, fatty acids and associated nutritional factors are included.

The active components in food supplements can be divided tentatively into two broad categories (Marks, 1989). One category comprises components with safety levels of at least 50 times the RDA, where there is no clear indication of serious reactions above that level, and the second comprises components with a safety level 50 times lower than the RDA, and in which possible adverse effects can be expected from an overdose or people at risk. Using the criteria in the inventory, we placed the following compounds in the second category:
1. Of the water-soluble vitamins, vitamin C is potentially harmful to people with a disturbed iron metabolism such as hereditary hemochromatosis. A high intake of folate (vitamin $B_{11}$) can mask the symptoms of a vitamin $B_{12}$ deficiency.
2. Of the fat-soluble vitamins, vitamins A and D have a relatively low margin of safety. A vitamin A intake of about eight times the RDA by pregnant women has been associated with birth defects. Children also appear to be particularly sensitive to hypervitaminosis D. A high intake of vitamin E is contra-indicated for people receiving anti-coagulant therapy.
3. Among the major minerals, especially iron can cause chronic adverse effects in individuals with hereditary hemochromatosis (both homo- and heterozygotes) or in those who take iron supplementation on a regular basis. Especially men over 20 years and postmenopausal women may be at risk of developing atherosclerotic diseases as a result of increased iron-induced oxidative stress. A maximum intake of 2-4 times the RDA is advised for zinc. A high calcium intake (i.e. more than twice the RDA) can cause several adverse effects, like gastrointestinal disturbances and constipation. Finally, the safety margin of selenium (a trace element) is very low.
4. Of the associated nutritional factors, special attention has to be paid to ß-carotene. This is because of an increased incidence of lung cancer among male smokers with a constant consumption of ß-carotene in doses more than ten times the RDA, compared to smokers who received a placebo.
5. The safety of the hormones dehydroepiandrosterone (DHEA) and melatonin has yet to be determined, but adverse side-effects have been reported.

When interpreting the data, one must consider that an increased intake of one nutrient may have consequences for the level of, or interaction with (an) other nutrient(s), and that imbalances can be created easily. One example is the reduction in magnesium and iron

absorption by certain forms of calcium supplements. Another is the occurrence of a copper deficiency when the zinc intake is high due to zinc displacing copper in enzymes.

# 1 Introduction

This study is performed on behalf of the Ministry of Health, Welfare and Sport, (Directorate for Public Health, Section Nutrition and Veterinary Policy) because of their responsibilities in observing the regulations of the Food and Drugs Act and in outlining policy concerning food products and -supplements. During the last decade, the availability of food supplements, such as vitamin pills, hormones, herbs, etc is strongly increased because of an increasing awareness of the relationship between nutrition and health in the general population. Besides pharmacies, supplements can be obtained from normal alimentary shops and even by Internet sources. This last possibility opens a world-wide market to the consumer which is in principle not controllable by the regulatory authorities.
Not only the amount of supplements has increased, but also an increasing *variety* of preparations is offered. This category of food supplements is also a relatively new area for the Regional Inspections of Public Health.
Therefore in this report a first attempt is made to summarize and classify the active components in food supplements as they are offered in the local shops but also on Internet sources. This report contains information both on the minimal required dose, the recommended and the toxic dose of components as on the possible adverse effects of deficiency. In this report herbal supplements were not included since a separate report has recently been published.[1]

The present report is the first result of our survey until October 1999. It will be clear that the information, especially on the toxic effects, is not yet complete. Furthermore, the list of active components will be enhanced continuously in the future and also new information on the present list of compounds will be included in later versions of this report.

# 2 Active components

In this report a classification has been made of the active components in food supplements. Only chemically well-defined components have been considered, not the supplements of herbal origin and the amino acid containing supplements. Of the hormone preparations, melatonin and dehydroepiandrosterone (DHEA) are discussed because of some recent publicity in the Netherlands.
We have chosen for a distinction in properties and quantities of the components instead of a division according to level of adverse effect or toxicity to make it possible to use this report as a quick reference guide. In each category, the compounds which are ‘commonly’ found in most of the supplements are included. To put the data in perspective of the toxic dose, an inventarisation of the ‘observed dose in supplements’ is made by visiting dietary supplement stores on the Internet and by obtaining data from supplements in local stores.

A division in the following categories has been made:
- water soluble vitamins (appendix I)
- fat soluble vitamins (appendix II)
- major minerals (appendix III)
- trace elements (appendix IV)
- hormones (appendix V)
- fatty acids (appendix VI)
- associated nutritional factors (appendix VII)

For each component, extensive information has been collected in a table.
In table 1, an overview is given of the active components which have been considered in this report with reference to the tables in the appendices.

*Table 1: overview of the active components discussed in the appendices*


| water soluble vitamins (appendix I) | | table | page |
|---|---|---|---|
| thiamin | (vitamin $B_1$) | 2 | 30 |
| riboflavin | (vitamin $B_2$) | 3 | 31 |
| niacin | (vitamin $B_3$) | 4 | 32 |
| pantothenic acid | (vitamin $B_5$) | 5 | 33 |
| vitamin $B_6$ | | 6 | 34 |
| biotin | (vitamin $B_8$) | 7 | 35 |
| folate | (vitamin $B_{11}$) | 8 | 36 |
| vitamin $B_{12}$ | | 9 | 37 |
| ascorbic acid | (vitamin C) | 10 | 38 |
| | | | |
| fat soluble vitamins (appendix II) | | Table | page |
| vitamin A | | 11 | 39 |
| vitamin D | | 12 | 40 |
| vitamin E | | 13 | 41 |
| vitamin K | | 14 | 43 |
| | | | |
| major minerals (appendix III) | | Table | page |
| calcium | | 15 | 44 |
| magnesium | | 16 | 45 |
| potassium | | 17 | 46 |
| iron | | 18 | 47 |
| zinc | | 19 | 48 |
| | | | |
| trace elements (appendix IV) | | table | Page |
| copper | | 20 | 49 |
| cobalt | | 21 | 50 |
| iodine | | 22 | 51 |
| fluoride | | 23 | 52 |
| chromium | | 24 | 53 |
| molybdenum | | 25 | 54 |
| selenium | | 26 | 55 |

*table 1 – continued-*


| hormones (appendix V) | table | Page |
|---|---|---|
| melatonin | 27 | 56 |
| DHEA | 28 | 57 |
| | | |
| fatty acids (appendix VI) | table | Page |
| omega 6-fatty acids | 29 | 58 |
| omega-3 fatty acids | 30 | 59 |
| | | |
| associated nutritional factors (appendix VII) | table | Page |
| quercetin | 31 | 60 |
| lipoic acid | 32 | 61 |
| choline | 33 | 62 |
| coenzym Q-10 | 34 | 63 |
| carnitine | 35 | 63 |
| inositol | 36 | 64 |
| creatine | 37 | 64 |
| glucosamine | 38 | 65 |
| lycopene | 39 | 65 |
| ß-carotene | 40 | 66 |

# 3 Results

Marks[2] considered that, on the basis of the reviewed information, active components may be divided into two broad categories:
A. Compounds with a safety level at least 50 times higher than the recommended daily allowance (RDA). From these compounds no serious adverse reactions can be expected.
B. Compounds with a safety level of about 10-50 times the RDA or lower. These compounds can cause serious irreversible adverse reactions, dependent of the dose and often influenced by the health status of the individual.
Most of the compounds discussed in this report fall in category A. The vitamins A, C, D, E, folate and calcium, zinc, selenium, iron, and β-carotene belong to category B because of reported adverse effects or toxicities, or because of an increased risk for certain groups.

The toxicology data of the vitamins indicate that a high intake of vitamin C is safe for healthy persons but may be harmful under conditions of a disturbed iron homeostasis and a high intake or body store of iron.[25,26] An excess of vitamin C can cause an instantaneous release of unreactive $Fe^{3+}$ from ferritin or transferrin and convert $Fe^{3+}$ to the toxic $Fe^{2+}$-form which can generate toxic amounts of free radicals. It is estimated[3] that about 10% of the Caucasians in Europe have a gene for iron overload. So, this might be a serious, under-estimated side effect in a lot of people.

The vitamins A and D are relatively toxic. Because of their fat-soluble properties, they will be stored and accumulated in adipose tissues. Intakes of vitamin A of 25 times the RDA are thought to be potentially intoxicating.[27,34,35] Intakes of 7-8 times the RDA in pregnancy have been shown to cause congenital malformations and mental retardation in offspring[85]
Hypervitaminosis A causes muscle and joint pains, headache, skin disorders and liver disfunction. Daily doses of vitamin D greater than about ten times the RDA (25 μg) are not recommended. Especially young children seem to be susceptible for hypervitaminosis D.[26]
In the Netherlands, the Commodities Act Exemption Regulation (1994) for vitamin supplements restricted the dose of retinoids in vitamin A pills because of the low safety ratio to 1.5 times the RDA (1200 μg). The daily dose of vitamin D is restricted to 5 μg for the general population; for children under 6 years and pregnant and lactating women the dose is restricted to 15 μg.

Vitamin E is relatively non-toxic for healthy persons. However, a high dose of vitamin E may increase the anti-coagulant effects of phylloquinone (vitamin K) antagonists and hence are contraindicated during anticoagulant therapy.[6,41,43] Furthermore supplementation of vitamin E alone can be the cause of the chain-breaking effect in the detoxification of oxygen radicals.

As for the vitamins A and D, the difference between the recommended intake level for folate and the intake level at which adverse effects cannot be ruled out is very small. Currently, an upper daily intake of 1,000 mg folate is recommended because of the masking of a vitamin $B_{12}$ deficiency with a higher intake.[87]

A modest increase in calcium intake should be safe for most people. However, a total calcium intake over 2 g/day (~2,5 times the RDA) can produce adverse effects such as gastrointestinal disturbances, constipation and, at a calcium intake of greater than 4 g/day, high blood calcium levels and severe renal damage.[47]

The margin between the safe zinc intake level (20-30 mg/day) and the recommended amount for zinc (9-10 mg) is very small, particularly in people with low copper intake. Zinc competes with copper as cofactor in enzymes and it can also induce metallothioneins (non-enzymatic metal-binding proteins), which inhibit the absorption of copper in the intestine.[50] So, adverse interactions between copper and zinc can occur even where the proportion between these two elements in the diet is relatively low.

The precise threshold for adverse effects of supplemental iron is not known and is probably also dependent on intake of other minerals (e.g. manganese, zinc and protein). However, chronic intake of high iron can result in excessive body iron stores and in the generation of toxic amounts of free radicals resulting in organ damage (liver, pancreas, heart, brain). Normal iron intakes can lead to similar adverse effects in people who are homo- or heterozygotes for hemochromatosis. This hereditary disease is characterized by an increased iron overload also under normal dietary conditions. Since it is estimated that about 10% of the population is heterozygous[3], iron supplementation should be avoided for men and postmenopausal women. A combined high intake of iron and vitamin C should be avoided by these people.

For selenium, the difference between the RDA and the safety level is relatively small. The upper limit of the RDA is 150 µg whereas 200 µg appears to produce adverse effects.[4,5]. However, other investigators report that a level up to 1600 µg is safe[6]. Early symptoms of selenium intoxication are fatigue and gastrointestinal disturbances whereas nail and hair abnormalities occur at doses over 6 times the RDA.

Carotenoids, such as ß-carotene are thought to have beneficial effects in preventing various diseases. Chronic consumption (3-5 yr) of 20-30 mg ß-carotene (10-15 times the RDA), however, caused an increased relative risk of lung cancer in smokers compared to smokers who received a placebo[7,8]. Therefore, chronic intake of high doses of ß-carotene have to be avoided by these people.

Melatonin is a neurohormone with a circadian pattern. In the U.S.A., it is sold over the counter in relatively high doses (300 µg up to 3.0 mg). In the Netherlands, melatonin supplements up to a dose of 100 µg per supplement are allowed which are thought to be harmless. There is lack of information on the toxicology of this hormone.[66] Some side effects are reported (hypotension, headaches, nightmares) but long-term side effects or interactions with drugs or nutrients are not known. Melatonin is possibly a strong antioxidant.
For DHEA (dehydroepiandrosterone), both an androgen and estrogen precursor, evidence of a beneficial effect on aging or disease is conflicting in the literature.[67] Some adverse (irreversible) effects as deepening of the voice and excessive hair growth in women have been reported.[67]

High dosed supplements (i.e. a dose higher than the RDA and relatively close to the adverse effect level) are mainly found in 'single component' supplements from the U.S.A..
Remarkable is the high selenium dose in some supplements of the U.S.A., up to the possible adverse effect level (200 µg). Also in the U.S.A., a dose of twice the RDA of magnesium is found in multi-component supplements although the (long term) toxicity of a high intake of magnesium is unknown.

Supplement usage in The Netherlands

From the three Food Consumption Surveys in The Netherlands held in 1987/88, in 1992 and in 1998, the following consumption patterns can be deduced. In 1987/1988, 17.2 % of the Dutch population takes supplements. This percentage has increased from 21.8 % in 1992 up to 24.1 % in 1998. A possible explanation for this increase might be that more attention has been paid to supplements and nutrition in commercials and/or the increased supply of supplements in food stores. In 1992, fluor supplements were used most often (6.8%); supplements with vitamin A and D and multiple vitamin-mineral supplements were used by 4.7% of the people, a vitamin C supplement was used by 4.3% and garlic-, vitamin B-, calcium- and brewer's yeast supplements were used by less than 4% of the population.
Also a significant relationship exists between age and supplement use: 76.4 % of the children aged 1-4 years uses supplements, adolescents use supplements less often (9%) whereas the proportion increases with age to 26.1 % in the group aged 50-65. The high usage among the young children can be explained by the current recommendations for the use of fluor and vitamin D tablets for this group. Also a significant relationship exists between sex and supplement use: women use supplements more often than men (24.7% and 18.5%, respectively). In general, people in the western regions of the Netherlands use supplements more often than people living in the southern parts (27.2% and 17.8% respectively). However, no relationship has been found between use of supplements and income in The Netherlands which is in contrast to the U.S.A. where the use of supplements increases with increasing income. [9-11]
The effects of age, sex, regional differences and social class on supplement use are also found in other countries (U.S.A., England, Australia). [9-15] The results of the use of supplements in the third national Food Consumption Survey[16] (1998) show some differences compared to 1992. The use of vitamin 'A and D' and fluor supplements is decreased as compared to 1992 (3.4 % compared to 4.7% and 5.5% compared to 6.8 % in 1992 respectively). The use of vitamin C supplements is nearly the same (4.3% compared to 4.4 % in 1998). Multivitamin supplements and the category 'miscellaneous supplements'(for example garlic-, calcium- and brewer's yeast supplements) are used more often (9.5% compared to 4.7% in 1992 and 10.8% compared to 4% in 1992 respectively).

Supplement usage in the U.S.A.

Vitamin supplement usage among the U.S. population has increased from 20 % of the population in the early 1970s to an estimated 40 % in 1996. Multiple vitamin-mineral supplements are used most often (7-14 %), and single-component supplements are used less often (vitamin A 1.2 %; vitamin C 7.6 %; and vitamin E 4.1 %).
Although several adverse effects have been associated with megadoses of antioxidant vitamins, most are single case reports or case series.[17]

The third National Food Consumption Survey in The Netherlands (Voedselconsumptiepeiling (VCP) 1998): intake of vitamins and minerals from food

The level of intake of vitamins, minerals and other components from the normal diet is obviously also important in determining the level at which adverse effects occur in individuals who take dietary supplements. Therefore, some general results of the most recent National Food Survey in the Netherlands (1998)[16,18] will be discussed here briefly with respect to the intake of vitamins and minerals from food products:

- vitamins:

The intake of vitamin B1, B2, C and E is higher than the RDA for all age groups. The intake of vitamin B6, in absolute sense, is adequate but when related to the protein intake especially the young age groups don't meet the RDA. Adolescents have a lower vitamin A intake than the recommended allowance. Infants and the elderly have a higher (dietary) requirement for vitamin D because of less sun exposure. For all other age groups, the vitamin D intake is sufficient (at least the RDA).

- minerals:

The average intake of calcium, phosphorus and magnesium is higher than the recommended daily allowance (RDA). The intake of iron in adolescents and women is lower than the RDA. This is also true for the intake of copper in men and women and of selenium in women. With increasing age, the intake of selenium decreases. The intake of zinc in adolescents is also lower than the RDA.

# 4 Conclusions

In this report, an overview of active components has been made which are frequently found in food supplements. The less well defined preparations from herbal origin and the amino acid-containing supplements are not taken into account.
Based on the difference between the RDA and possible toxic effects, a general distinction in the active components, according to Marks[2], has been made. Some components are relatively safe at a high intake (> 50 times the RDA, category A) but others show toxic effects at an intake lower than 50 times the RDA (category B).
Based on the data in this report, we have classified the following compounds in category A: vitamin $B_1$, vitamin $B_2$, vitamin $B_3$, vitamin $B_5$, vitamin $B_8$, folate, vitamin $B_{12}$, vitamin K, cobalt, iodine, fluoride, chromium, molybdenum, omega-6-fatty acids and omega-3-fatty acids.
In category B the following compounds have been put because of their reported adverse effects or toxicity, or because of an increased risk at high intakes for risk groups: the vitamins A, C, D, E, folate, calcium, zinc, selenium, iron, and β-carotene. At present, most worrisome is the high intake of iron (and/or vitamin C) by individuals, hetero- or homozygote for the iron overload disease hemochromatosis. Especially chronic adverse effects can be expected even with moderate intakes of iron. These individuals should avoid a high intake of iron, especially in combination with vitamin C. We are currently assessing the prevalence of homo- and heterozygosity for hemochromatosis among individuals with a history of cardiovascular diseases.
No chronic human toxicity data are known or could be found for quercetin, lipoic acid, coenzym Q-10, carnitine, inositol, creatine, glucosamine and lycopene.
With respect to the minerals magnesium, potassium and copper, it is hard to set an upper safe limit because the interaction of these minerals with other minerals is very important and is beyond the scope of this paper.
With respect to the hormones melatonin and DHEA, adverse effects are reported but the effects of a chronic high intake in humans are not yet investigated.

One has to bear in mind that, although in principle no deficiency of a certain compound is to be expected, a large dose of a specific compound can cause imbalances within a class of compounds and, as a result, can lead to a deficiency of one essential component. Examples can be found in the group of minerals (calcium, magnesium, iron, zinc), trace elements (chromium, selenium, copper, cobalt) and antioxidants (vitamin C, E, carotenoids).
Besides problems with overdose, certain effects of normal or somewhat elevated doses of vitamins and/or minerals can be expected in certain groups at risk.
These risk groups include pregnant women for vitamin A, children for vitamin A and D**,**

folate for $B_{12}$-deficient people, individuals with hemochromatosis for iron and vitamin C, patients receiving anti-coagulant therapy for vitamin E, patients with chronic renal failure and kidney stones for calcium, and smokers for β-carotene.
With respect to the dose of components in supplements, in the Netherlands no alarming high levels have been found.

In conclusion, vitamin A and D, zinc and selenium are toxic at relatively low intakes, also for healthy persons. Special risk groups can be identified for iron, vitamin C and E, folate, calcium and ß-carotene. The safety of the hormones melatonin and DHEA (and dehydroepiandrosterone) has not been investigated thoroughly, so special care should be taken with the use of these compounds. More research and attention is needed to get quantitive data on the intake of the mentioned components in these risk groups and the health consequences for them.

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# References-II

Information about the composition of the supplements derived from the Internet, pages: (alphabetical order)(all visited between December 9th and December 15th, 1998)


| | |
|---|---|
| Allergy Research Group | http://www.emersonecologics.com |
| Body Wise | http://www.bodywise.org |
| Herbal Dave | http://www.herbaldave.com |
| IPS (Immediate Pharmaceutical Services) | http://www.ipsrx.com |
| Kivita | http://www.samik.co.kr |
| Life Extension | http://www.lef.org |
| Life Plus | http://www.lifeplus.com |
| Life Services | http://www. lifeservices.com |
| Manna Nutrition | http://www.liquidcreatine.com |
| Mineral Connection | http://www.mineralconnection.com |
| Netrition | http://www.3.netrition.com |
| Nutraceutix/Biopower | http://www. biopowr.com |
| Omega Nutrition | http://www. prolithic.com |
| Professional Supplements | http://www.archemed.com |
| Sigma-Tau Pharmaceuticals | http://www.sigma-tau.it |
| Supplements Online | http://www.supplementson-line.com |
| Twinlab | http://www.netrition.com |
| VirtuVites | http://www.virtuvites.com |
| Vitamin Power Company | http://www.healthdepo.com |
| Vitamins Power | http://www.vitaminpower.com |
| Vitanet | http://www.healthstyle.com |
| Worldwide Labs | http://www. webadprod.com |

# Appendices

**Explanation of the tables in appendices I-VII**

**Nomenclature:** the nomenclature policy is based on 'Generic descriptors and trivial names for vitamins and related compound: recommendations (1976)' by the International Union of Nutritional Sciences Committee on Nomenclature[19], which is consistent with the Recommendations of the Commission on Biochemical Nomenclature IUPAC-IUB and the committee on Nomenclature of the American Institute of Nutrition.
On the right side, between parenthesis, the way the component is found in supplements most often is mentioned. The cursivated component is the component as described in 'observed dose in supplements' (see below).

**Minimum:** this is the quantity of the nutrient that must be supplied in the diet in order to satisfy the metabolic need; it includes factors associated with digestion, absorption and cellular bioavailability.[20]

**RDA:** When available, the Dutch recommended dietary allowances (RDA) are given.[4] If not, the American RDAs are used.[21,22] Recommended Dietary Allowances (RDAs) are the levels of intake of essential nutrients, that, on the basis of scientific knowledge, are judged by the National Health Council (the Netherlands) or the Food and Nutrition Board (USA) to be adequate to meet the known nutritional needs of practically all healthy persons (mean requirement level plus two times the standard deviation). When known, RDAs for men (M) and women (F) are given separately.
***Note:*** At this moment, in the US new dietary reference intakes (DRIs) are being made which are intended to replace the RDAs (1989). The DRIs reflect a shift in emphasis from preventing deficiency to decreasing the risk of chronic disease through nutrition. Instead of a single value, the DRIs will encompass:
- estimated average requirement (EAR): the intake that meets the estimated nutrient need of 50% of the individuals in a specific group
- recommended daily allowance (RDA): the intake that meets the nutrient need of almost all (97-98%) of the healthy individuals in a specific age and gender group. If individual variation in requirements is well defined, the RDA is set at 2 standard deviations above the EAR. If sufficient data are not available, the RDA is set at 1.2 x EAR.
- adequate intake (AI): when sufficient scientific evidence is not available to estimate an average requirement, adequate intakes will be set.
- tolerable upper intake level (UL): the maximum intake by an individual that is unlikely to pose risks of adverse health effects in almost all healthy individuals in a specified group.

**Toxicity:** the exact level at which persons develop symptoms in response to overconsumption of a certain compound is difficult to define. The size and age of individuals, the duration of the supplementation periods, and the quantity and form of the compounds consumed can greatly affect sensitivity. For certain components, the level of toxicity is highly speculative or

is not known in humans. When available, a tolerable upper intake level is given. This is the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population. When the intake increases above this level, the risk of adverse effects increases.[23]

No special attention has been paid to whether the produced effect is reversible or irreversible and if the component produces local or systemic toxicity.

With respect to the minerals, it is difficult to define a total toxic dose because both the duration of exposure and the level of exposure is important. Some minerals can produce adverse effects after an acute single overdose but are relatively safe when ingested at a lower concentration during a longer time period. If known, information about this aspect and the possible adverse effects is given.

**Observed dose in supplements:** All the supplements are tablets or capsules.
First, the brand name is mentioned, followed by the facturer's name (if known) or the supplier's name and the year of sale. The suggested daily intake according to the manufacturer is indicated and the serving size is 1 tablet/caps unless mentioned otherwise (e.g. 40 mg in 4 tablets). The selection is 'at random', trying to give a good overview of the available quantities and doses and of the suggested dose of the manufacturers.
Most of the time, the compound is a constituent of a supplement with more active components (e.g. multivitamin supplement). If the supplement is a single-component supplement, it is marked with an asterisk (for example: 500 mg vitamin C supplement *)

**Dietary source:** food products or categories are mentioned which are a (relatively) rich source of the component.

**Function:** a general description of the effect or function in the human body is given.

**Deficiency symptoms:** a broad description of early and/or late symptoms are listed which can occur when the minimum requirement is not reached.

***Note:*** when no (recent) information could be found about an aspect of a component or the aspect does not apply for the component, a hyphen is used.

# Appendix I Water soluble vitamins

*Table 2: thiamin*

| | |
|---|---|
| thiamin (formerly known as vitamin $B_1$) | (*thiamin-HCl*) |
| Minimum requirement | 0.8 mg[24]<br>1.0 mg[25]<br>70-95 µg/Megajoule[4] |
| Recommended daily allowance (RDA) | M: 1.1 mg<br>F: 1.0 mg<br>note: requirement is coupled to energy intake.<br>median intake in the U.S. is 2 mg/d. The ninety-fifth percentile of intake from both food and supplements is approximately 6.1 mg in the U.S.[23] |
| Toxic dose | the toxic potential of thiamin appears to be low, particularly when it is administered orally. Large parenteral doses (100-500 mg) are generally wel tolerated. Only after several injections, by different routes, of doses exceeding by more than 100-200 fold the RDA have few, if any, toxic effects ascribed to allergic reactions been reported.[20,26]. |
| Observed dose in supplements | 1.1 mg, 1.5 mg (Kruidvat en Etos bruistablet, 1996)<br>4.5 mg (Supradyn complex forte, Roch, 1996)<br>15 mg (Pharmachemie Vit.B complex forte, 1996) |
| Dietary source | whole wheat products, porc, nuts, liver, potatoes. |
| Function | plays a key role in the body's metabolic cycle for generating energy; aids in the digestion of carbohydrates; essential for the normal functioning of the nervous system, muscles and heart; stabilizes the appetite, promotes growth and good muscle tone, facilitates carbohydrate metabolism and may be deficient in those on a high sugar diet. |
| Deficiency symptoms | may lead to the loss of appetite, weakness and feeling tired, insomnia, mental depression, rapid heart beat, constipation, heart- and gastrointestinal problems, in extreme: beriberi. |

*Table 3: riboflavin*

| | |
|---|---|
| riboflavin (formerly known as vitamin $B_2$ or vitamin G) | (*riboflavin*) |
| Minimum requirement | 1.1 ,mg[4,24] |
| Recommended daily allowance (RDA) | M: 1.6 mg<br>F: 1.3 mg<br>note: requirement is coupled to energy intake. |
| Toxic dose | high oral dosages of riboflavin are not toxic, probably due to the relatively poor absorption at high intake levels. No adverse effects in humans have been reported. Studies with animals indicate that dosages as great as 100 times allowance levels have negligible risks of toxicity.[26] |
| Observed dose in supplements | 4.2 mg (OMNI-PLEX, Essential Organics, 1996)<br>5 mg in 4 tabl. (TVM 49, Life Plus, 1998)<br>25 mg in 4 tabl. (Multi Four+, Orthica, 1996). |
| Dietary source | liver, milk, cheese, eggs, green vegetables. |
| Function | necessary for carbohydrate, fat and protein metabolism, also in the formation of antibodies and red blood cells, maintains cell respiration; necessary for the maintenance of good vision, skin, nails and hair, acts particularly closely with vitamins B6 and B3 and selenium. |
| Deficiency symptoms | burning or gritty eyes, sore tongue, cataracts, dull or oily hair, eczema or dermatitis, split nails, cracked lips. |

*Table 4: niacin*

| | |
|---|---|
| niacin (formerly known as vitamin $B_3$) | (*nicotinamide)* |
| Minimum requirement | 12 mg (USA)[21], no dutch recommendations |
| Recommended daily allowance (RDA) | 18 mg (USA)[21], no dutch recommendations |
| Toxic dose | in humans, high dosages (2-4 g/ day) of nicotinic acid (protein bound form of niacin, mainly in plants), cause vasodilatation, itching, nausea, vomiting and headaches, whereas nicotinamide (nicotinic acid amide, animal tissues) only rarely produces these reactions. Nicotinamide dosages of 50-100 times RDAs (900 mg-1800 mg) can be considered safe for most people. Available information on the tolerance of animals for niacin is scant but suggest that daily doses greater than 350-500 mg nicotinic acid equivalents per kg body weight can be toxic[26] (24,5 - 35 g for the average person). |
| Observed dose in supplements | 1 mg (Kruidvat, multivitamins, 1996)<br>25 mg. in 3 tabl. (Nutra Source 100, Vitamin Power Company, 1998)<br>50 mg (Super B-complex 50, Vitamin Power Company, 1998)<br>90 mg (Ultra Potency Multiple 90, Vitamin Power Company, 1998). |
| Dietary source | meat, eggs, fish, milk, whole grains.[26] |
| Function | promotes the function of the central nervous system and of the digestive system. Needed for the energy production by cells. |
| Deficiency symptoms | pellagra, gastrointestinal disturbances, insomnia, skin disorders, loss of appetite, muscular weakness. |

*Table 5: pantothenic acid*

| pantothenic acid | (*d-calciumpanthothenate*) |
|---|---|
| Minimum requirement | 2 mg (USA)[21], no dutch recommendations |
| Recommended daily allowance (RDA) | 4-7 mg (USA)[21], no dutch recommendations<br>produced by intestinal micro-organisms, deficiencies in humans not known. |
| Toxic dose | generally regarded as being non-toxic but a few reports indicate diarrhea occurring in humans consuming 10-20 g of this vitamin per day[26] but it seems safe for humans at dosages of at least 100 times RDA (400-700 mg).[80] There is not sufficient scientific data to set a tolerable upper intake level for pantothenic acid.[20] |
| Observed dose in supplements | 50 mg (Super-Vite, Vitamin Power, 1998)<br>90 mg (Ultra Potency Multiple 90, Vitamin Power Company, 1998)<br>500 mg (Panthotenic Acid, Life Extension Products, 1998) *. |
| Dietary source | liver, milk, meats, eggs, whole grains, fish, vegetables.[26] |
| Function | pantothenic acid mainly is incorporated in the body into coenzyme A, which has many metabolic roles in the cells. For example, it is essential to the synthesis of fatty acids and membrane phospholipids as well as to the oxidative degradation of fatty acids and amino acids. |
| Deficiency symptoms | skin abnormalities, retarded growth, digestive disturbances, stomach stress, muscle cramps. |

*Table 6: vitamin $B_6$*

| vitamin $B_6$ | (*pyridoxine-HCL*) |
|---|---|
| Minimum requirement | 1.0 mg[4,24]<br>1.0-1.5 mg (females)[4] |
| Recommended daily allowance (RDA) | M: 1.4 mg<br>F: 1.1 mg |
| Toxic dose | the acute toxicity is very low (1 g/kg is tolerated well) but toxicity may occur with chronic daily doses of 200-500 mg or more and it should always be under medical supervision.[27,28]<br><br>daily dosages of 500 mg vitamin B6 have been used for humans (treatment of premenstrual tension in women) for periods of several months without significant adverse effects. Larger dosages (500 mg to 6 g per day) have produced reversible neuropathies after chronic use.<br>Levels as great as 100 times RDAs (110-140 mg) can be used safely for most people.[26]<br>The Food Advisory Committee (FAC) adviced that an intake from dietary supplements should not exceed 10 mg/d. The subject of an upper safe level of vitamin B6 therefore requires further careful, scientific consideration.[80] |
| Observed dose in supplements | 1 mg (Davitamon Total, 1996)<br>6 mg in 3 tabl. (Support Tabs, Life Plus, 1998)<br>75 mg (Vita-Min 75 (vegetarian formula), VirtuVites Supplements, 1998). |
| Dietary source | meat, fish, vegetables, bananas, wholegrains, seeds and nuts, bread. |
| Function | acts with other B complex vitamins, zinc and magnesium, required for the metabolism and synthesis of proteins, needed for utilizing essential fatty acids, keeping levels of the female hormone oestrogen stable, essential for efficient nerve transmission, protein digestion and utilisation, involved in the maintenance of the circulation, the skin, the immune system and the production of neurotransmitters in the brain, helps the absorption of B12, maintenance of fluid balance in the body. |
| Deficiency symptoms | alterations in the function of the nervous system evidenced by ECG are among the earliest symptoms of vitamin B6-defiency. Severe deficiency may produces seizures, dermatitis, glossitis and anemia. These deficiencies are rare, but subclinical deficiencies may exist, especially in women and the elderly. |

*Table 7: biotin*

| | |
|---|---|
| biotin (formerly known as vitamin H, vitamin B8 or coenzym R) | (*biotin)* |
| Minimum requirement | the adequate intake is 30 µg/d.[20] |
| Recommended daily allowance (RDA) | 100-200 µg (USA)[21] |
| Toxic dose | generally regarded as being non-toxic. Adverse effects of large dosages of biotin have not been reported in humans given the vitamin orally. There is insufficient data on which to base a tolerable upper intake level.[20] |
| Suggested dose manufacturer | 30 µg (Super-Vite, Vitamin Power, 1998)<br>75 µg (Vita-Min 75 (vegetarian formula), VirtuVites Supplements, 1998)<br>90 µg (Ultra Potency Multiple 90, Vitamin Power Company, 1998)<br>150 µg (NEW-TON, Sandripro, S.A. Bruxelles, 1996). |
| Dietary source | egg yellow, liver, soya beans, peanuts, carrots, cauliflower. Note: produced in considerable quantities by intestinal microflora. |
| Function | co-enzyme which works with several B-vitamins. Part of many enzyme systems and it is involved in the conversion of amino acids to protein. Involved in the production of energy from carbohydrates, fatty acid metabolism and the conversion of folic acid to a biologically active form. |
| Deficiency symptoms | dry skin, poor hair condition, leg cramps, poor appetite, eczema, dermatitis, depression. |

*Table 8: folate*

| folate | (*pteroylmonoglutamic acid : folic acid)* |
|---|---|
| Minimum requirement | 50 µg[29] |
| Recommended daily allowance (RDA) | M: 200-300 µg<br>F: 200-300 µg<br>200 µg (M), 180 µg (F) in the USA.[29]<br>300 µg (M + F) in Germany and France.[29]<br>desired folate intake:<br>- 400 µg/d of supplemental folic acid for women planning a pregnancy to prevent the occurrence of neural tube defects<br>- a total intake of at least 350 µg/d for the general adult population to maintain 'normal' plasma homocysteine levels.[29] |
| Toxic dose | generally regarded as being non-toxic. Other than a few cases of apparent allergic reactions, the only proposed adverse effect in humans (interference with the enteric absorption of Zn) is not supported with adequate data.<br>Levels of at least 2000 times RDAs (400-600 g) are safe.[26]<br>In the Netherlands, currently a safe upper limit of 1,000 mg is desirable because of the masking of haematological disturbances due to vitamin B12 deficiency with a (too) high folate intake.[30]<br>note: the bioavailability of naturally occuring folate is about 50% lower than that of folate from supplements.[29] |
| Observed dose in supplements | 75 µg ( Multivitamins, D.A., 1996)<br>100 µg (Multivitamins, Vitalia, 1996)<br>1000 µg (Mega Vitamin Kit, Club Vitamin, 1998). |
| Dietary source | liver, nuts, whole wheat products, leafy green vegetables. |
| Function | necessary for DNA & RNA synthesis, which is essential for the growth and reproduction of all body cells, essential to the formation of red blood cells by its action on the bone marrow, facilitates amino acid metabolism, helps to regulate histamine levels in the body.<br>Note: recent research indicates that folic acid may play a protective role against heart disease due to its ability to lower homocysteine levels. |
| Deficiency symptoms | eczema, lack of energy, poor appetite, depression, macrocytic anemia. |

*Table 9: vitamin $B_{12}$*

| vitamin $B_{12}$ | (*cyanocobalamin*) |
|---|---|
| Minimum requirement | 1 µg[24] |
| Recommended daily allowance (RDA) | M: 2.5 µg<br>F: 2.5 µg |
| Toxic dose | generally regarded as being non-toxic. A few cases of apparent allergic reactions have been reported in humans. Upper safe limits are highly speculative. According to the Food and Nutrition Board (US), there is insufficient evidence to substantiate adverse health effects from high intake of vitamin B12 as obtained from food or supplements.[20] It appears that dosages of at least as great as 1000 times RDAs are safe for humans and animals.[26] |
| Observed dose in supplements | 0,5 µg (Davitamon Total, 1996)<br>6 µg (Ultra Potency Multiple 90, Vitamin Power Company, 1998)<br>60 µg (Pharma B-12, Life Services, 1998) *. |
| Dietary source | meat, milk, cheese, eggs, liver, fish, bread. |
| Function | essential for red blood cell formation and for making the myelin sheath that insulates nerve cells and for making DNA. Works together with B11, needed for calcium absorption. |
| Deficiency symptoms | pernicious anaemia, growth failure in children, tiredness, neuritis, degeneration of spinal cord, depression. |

*Table 10: vitamin C: water-soluble*

| vitamin C | (*ascorbic acid*) |
|---|---|
| Minimum requirement | 50 mg[24] |
| Recommended daily allowance (RDA) | M: 70 mg<br>F: 70 mg<br>note: the RDA in the USA is 60 mg (1989), but currently the recommendations for vitamin C intake are under revision by the Food and Nutrition Board of the National Academy of Sciences. The RDA is proposed to be set at 120 mg/d, based on extensive biochemical, molecular, epidemiologic, and clinical data.[81] |
| Toxic dose | vitamin C is remarkably non-toxic. Excessive amounts of ingested vitamin C are poorly absorbed and almost completely excreted in the urine. Metabolic byproducts of ascorbic acid such as urate and oxalate may be increased at a high intake but data are conflicting.[31]<br>The only adverse effect that have been consistently observed in humans are gastrointestinal disturbances and diarrhea occurring at levels of intake nearly 20-80 times RDAs (1.4 -5.6 g). Intakes of 100-1000 times up allowance levels up to 10 g/day appear safe for healthy people[25,26]<br>but currently, strong scientific evidence to define and defend a safe upper limit for vitamin C is not available.[82]<br><br>Vitamin C will enhance iron absorption by maintaining iron in its reduced form. In cases of iron overload or impaired iron metabolism, increased vitamin C intake may be harmful by exerting prooxidant effects.[31,32]<br>At high intakes, it can also replace glucose in adverse glycation reactions resulting in cross-links between proteins.[33] |
| Observed dose in supplements | 35 mg (Multivitamins, Kruidvat, 1996)<br>60 mg (Multivitamins and Minerals, Vitalia, 1996)<br>500 mg (Vitamin C supplement, Solgar, 1998) *<br>1000 mg (Vita-C-1000-TR, time released, Life Plus, 1998) *. |
| Dietary source | new potatoes, (straw)berries, citrus fruits, leafy green cabbage-family vegetables (such as broccoli and cauliflower). |
| Function | a powerful antioxidant, facilitates absorbtion of iron from food, makes collagen, involved in synthesis of hormones, activating folic acid and has a protective effect for other vitamins (A, E, B). |
| Deficiency symptoms | frequent colds, bleeding or tender gums, easy bruising, slow wound healing, red pimples on skin (in extreme: scurvy). |

# Appendix II Fat soluble vitamins

*Table 11: vitamin A*

| | |
|---|---|
| vitamin A | (*retinol palmitate*, retinyl acetate) |
| Minimum requirement | 600 retinol equivalents (RE) (=600 µg retinol = 1998 IU) |
| Recommended daily allowance (RDA) | M: 1000 RE (=1000 µg retinol = 3330 IU)<br>F: 800 RE (= 800 µg retinol = 2664 IU) |
| Toxic dose | range of safe intake is relatively small. Intakes of 25 times the RDA are thought to be potentially intoxicating.[27,34,35]<br>Signs of hypervitaminosis A are muscle and joint paints, headache, skin disorders (erythema, eczema) and liver dysfunction.<br>Actual cases of hypervitaminosis A have been very rare at chronic doses less than ca. 9000 RE per day.[34] Children appear to be especially susceptible to hypervitaminosis A. A safe maximum daily intake for children is 750 RE/kg body weight.[86]<br>A rough, safe guideline is that an intake of 15 times the RDA is still safe, but during pregnancy, the intake should be limited to 3 or 4 times the RDA (or about 35-45 RE/kg body weight). [86,88] Intakes of ca. 25,000 IU/day (7500 RE, about 9 times the RDA) by pregnant women have been associated with birth defects.[26]<br>note: absorption of vitamin A from an emulsified solution in water proceeds faster and more complete than from an oil solution. Vitamin A containing aqueous supplements therefore pose a greater risk in terms of an overdose.[36] |
| Suggested dose manufacturer | 3000 IU (900 RE) in 3 tabl. (KIVITA, chewing tablets, 1998) (USA)<br>8000 IU (2400 RE) (Super Aytinal, Walgreens, 1998) (USA)<br>supplements in the Netherlands in 1994 varied from about 300 µg to 15000 RE as daily dose.[37] According to the Commodities Act Exemption Regulation for vitamin supplements (1994) in the Netherlands[38], the daily dose of 1200 µg retinoids in supplements may not be exceeded. |
| Dietary source | liver, butter, whole milk (-products), egg yolk, green vegetables. |
| Function | essential for growth, maintenance of visual function, reproduction and for differentiation of epithelial tissue.[39] |
| Deficiency symptoms | night blindness, increased susceptibility to infections; rough, dry, scaly skin; lack of tearing; defective teeth and gums' retarded growth. |

*Table 12: vitamin D*

| vitamin D | (*cholecalciferol (vitamin D3)*) |
|---|---|
| Minimum requirement | made by the body when exposed to sunlight.<br>not known[4] |
| Recommended daily allowance (RDA) | infants, aged 0-7 years: 10-15 µg (400 IU-600 IU)<br>children, aged 10-19 years: 2.5-5.0 µg (100 IU-200 IU)<br>M + F, aged 19-65: 0-2.5 µg (0-100 IU)<br>age 65+: 2.5-5 µg (100 IU-200 IU)<br>pregnant and lactating women: over 10 µg (400 IU) daily<br>note 1: RDAs: lower limit when sufficient exposure to sunlight<br>note 2: in the Netherlands, vitamin D suppletion is recommended recently by the Dutch Health Council for people over 75 years living in a home for the elderly, because the vitamin D intake from their food is not sufficient and for some elderly, exposure to the sun is little or absent. The recommended/desirable intake in this age group is 7.5 - 10 µg. |
| Toxic dose | because they are stored in adipose tissue, vitamins $D_2$ and $D_3$ have relatively high potentials for producing systemic toxicity after single overdoses. Children appear to be particularly sensitive to the hypervitaminosis. It can be exacerbated by high intakes of Ca and P and reduced by intakes of low Ca levels or of Ca-chelating agents.[26]<br>daily doses greater than 1000 IU (25 µg) are not recommended even though evidence shows that the currently accepted, no observed adverse effect limit of 50 µg (2000IU)/d is too low by at least 5-fold.[27,40,83]<br>signs of hypervitaminosis D are anorexia, gastro-intestinal distress, headache and hypercalcemia.[26]. |
| Suggested dose manufacturer | 100 IU (Ultra Minerals, VirtuVites, 1998)<br>400 IU (Ultra Potency Multiple 90, Vitamin Power Company, 1998)<br>1000 IU (Vitamin D3, Life Extension Products, 1998) *.<br>According to the Commodities Act Exemption Regulation for vitamin supplements (1994) in the Netherlands[38], the daily dose of 5 µg vitamin D (200 IU) in supplements may not be exceeded but for supplements especially for pregnant and lactating women and children up to 6 years, the daily admitted dose is 15 µg (600 IU). |
| Dietary source | fatty fish, egg yolk. |
| Function | improves absorption and utilization of calcium and phosphorous, required for bone and teeth formation; maintains a stable nervous system and normal heart action. |
| Deficiency symptoms | may lead to rickets (children), osteomalacie (adults), tooth decay, softening of bones, improper healing of fractures, lack of vigor, muscular weakness, inadequate absorption of calcium, retention of phosphorous in the kidneys. |

*Table 13: vitamin E*

| vitamin E | (*all-rac*-α-*tocopheryl acetate*, *all-rac*-α-tocopheryl succinate) |
|---|---|
| Minimum requirement | 9 mg α-TE[24]<br>0.4 mg α-TE / gram of polyunsaturated fatty acids (PUFA)[4]<br>4 mg α-TE / gram when almost no PUFA are consumed[4] |
| Recommended daily allowance (RDA) | M: 11.8 mg α-TE (= 17.6 IU)<br>F: 9.3 mg α-TE (= 13.9 IU)<br>0.67 α-TE / gram of PUFA[4]<br>note: no optimal amount has been established with certainty[41] |
| Toxic dose | there are several reviews of the literature concerning the safety of vitamin E. Conclusions: the use of supplements of vit. E at dosages from 200-1400 IU/d (about 13-160 times the current RDAs), administered for periods up to 4.5 y is safe.[42]<br>Unlike the other fat-soluble vitamins, vitamin E is not stored in the liver and this may account for its relatively low toxicity.[31]<br>There is a risk of adverse effects above intakes of 3000 IU vitamin E per day; among them are gastrointestinal complaints, creatinuria and impairment of blood coagulation.[41]<br><br>Vitamin E at high intakes affects the indexes of coagulation if vitamin K deficiency is also present. A vitamin K deficiency that is just tolerable and without symptoms may be exacerbated by administration of vitamin E so that symptoms become apparent. Clearly, vitamin E must not be given under these conditions which may have been caused by malabsorption or by anticoagulant therapy; alternatively, administration of vitamin E must be accompanied by concomitant administration of vitamin K.[6,41,43]<br>In normal subjects, alpha-tocopherol caused a dose-dependent inhibition of arachidonic acid-mediated platelet aggregation in vivo with an $IC_{50}$ (inhibitory concentration required for 50% inhibition) of 450 μmol/L, a value that greatly exceeds the range for plasma a-tocopherol content in normal subjects (15-40 μmol/L) or subjects taking supplemental a-tocopherol (30-120 μmol/L).[44]<br>A controlled trial to the potential for vitamin E supplements to affect platelet function and bleeding time found that 900 IU/d for 3 mo did not affect bleeding time or prothrombin time.[45] Recently, another well-controlled study in which 800 IU vitamin E was given daily for 1 mo to 32 healthy elderly confirmed again that there was no effect on hematologic or other biochemical parameters associated with bleeding.[46] |
| Suggested dose manufacturer | 400 IU (Preventive Plus Formula, Best Vitamins, 1998)<br>the most common supplement doses are 100, 200, 400 and 800 IU.[31] |

| | |
|---|---|
| Dietary source | vegetables and vegetable oils, wheat germ, fruits, meat, poultry, fish, nuts, seeds. |
| Function | intracellular antioxidant: protects polyunsaturated fatty acids in cell membranes from oxidative damage. Keeps selenium in the reduced state, helps heal scar tissue, oxygenate muscles and maintains immunity. |
| Deficiency symptoms | hemolytic anemia, abnormal fat deposits in muscles, dry skin, loss of reproductive powers, easy bruising, slow wound healing, infertility. |

*Table 14: vitamin K*

| vitamin K | (*menadione*, phylloquinones) |
|---|---|
| Minimum requirement | produced by healthy intestinal bacteria, so it is rarely deficient except in young infants (since the production of vitamin K by the intestinal flora is insufficient at a young age (0-3 months) and breast milk contains insufficient vitamin K) |
| Recommended daily allowance (RDA) | 70-140 µg (USA)[21] |
| Toxic dose | the toxic potential of the naturally occuring forms of vitamin K are negligible.[26] No known cases of toxicity in man. Little is known about the toxicity of the vitamin even in animals[27] but a safety ratio of about 15 times the normal intake has been recommended.[40]<br><br>the toxic treshold of the synthetic vitamer menadione appears to be at least 1000 times allowance levels.[26] Menadione appears to react with sulfhydryl groups on proteins.[27] |
| Suggested dose manufacturer | 25 µg (Super Aytinal, Walgreens co., 1998)<br>500 µg in 4 tabl. (TVM-49, Life Plus, 1998) |
| Dietary source | dairy products, wholegrain cereals, broccoli, spinach. |
| Function | needed for the formation of strong bones and for normal blood clotting. |
| Deficiency symptoms | hypocoagulability[4] |

# Appendix III Major minerals

*Table 15: calcium*

| | |
|---|---|
| calcium | (*calcium carbonate*; calcium phosphate) |
| Minimum requirement | 400-600 mg[25] |
| Recommended daily allowance (RDA) | M: 700-900 mg<br>F: 700-900 mg<br>note 1: the current RDA for calcium intake during pregnancy and lactation is 1,200 mg.<br>note 2: adequate vitamin D is essential for optimal calcium absorption. |
| Toxic dose | a modest increase in calcium intake should be safe for most people. A total calcium intake that exceeds 2,000 mg/day seems likely to produce adverse effects as gastrointestinal disturbances and constipation. At intakes of greater than 4,000 mg, high blood calcium levels, severe renal damage and calcium deposition can be produced. However, the physiology of calcium metabolism is tied together with phosphate metabolism and the function of vitamin D, along with the two regulatory hormones parathyroid hormone (PTH) and calcitonin. Effective therapeutic doses provide about 3,600 mg.[47] Subjects with an impaired vitamin D synthesis or who have a history of kidney stones may be at increased risk from higher calcium intakes (49). Iron absorption can be decreased by as much as 50 percent by many forms of calcium supplements but not by forms that contain citrate and ascorbic acid, which enhance iron absorption. Thus, increased intakes of specific sources of calcium might induce iron deficiency in individuals with marginal iron status. Population studies suggest that this is not a common or severe problem, but more study is needed. Whether calcium supplements interfere with absorption of other nutrients has not been thoroughly studied.[48] |
| Observed dose in supplements | 93 mg (Super-Vite, Vitamin Power, 1998)<br>600 mg in 4 tabl. (TVM-49, Life Plus, 1998)<br>1000 mg in 4 tabl. (Ultra Minerals, VirtuVites, 1998). |
| Dietary source | dairy products (e.g. milk and cheese) |
| Function | calcium is responsible for structural functions involving the skeleton (bones contain 98-99% of the body calcium) and soft tissues and regulatory functions such as neuromuscular transmission of chemical and electrical stimuli, cellular secretion, and blood clotting.[20] |
| Deficiency symptoms | decreased growth (in young), weight loss, reduced appetite, osteoporosis and osteomalacia. |

*Table 16: magnesium*

| | |
|---|---|
| magnesium | (*magnesium oxide*, magnesium aspartate, magnesium glycerophosphate, magnesium gluconate) |
| Minimum requirement | not known.[4] |
| Recommended daily allowance (RDA) | M: 300-350 mg<br>F: 250-300 mg |
| Toxic dose | not known.[4]<br>the maximum total safe daily intake seems to be 700 mg.[80]<br>intoxication occurring after oral administration of magnesium salts is rare but may be present in the face of renal impairment.[5] |
| Observed dose in supplements | 20 mg (Super-Vite, Vitamin Power, 1998)<br>80 mg (Ca-Mg supplement, Hema, 1996)<br>750 mg in 4 tabl. (Ultra Minerals, VirtuVites, 1998). |
| Dietary source | green leafy vegetables, dairy products, cereals, drinking water, nuts.[4] |
| Function | bones contain 60-70% of the body magnesium. Cofactor of several enzyme systems, it is apparently associated with phosphate in these functions. |
| Deficiency symptoms | neuromuscular irritability, calcification, cardiac and renal damage, retarded growth, anorexia. |

*Table 17: potassium*

| potassium | (*potassium chloride*, potassium gluconate) |
|---|---|
| Minimum requirement | 1600-2000 mg[25] |
| Recommended daily allowance (RDA) | 3500 mg (USA)[22] |
| Toxic dose | acute potassium toxicity may have similar effects as potassium deficiency, including heart failure, however it is rarely linked to diet. It tends to occur only in the event of kidney failure.<br>not established.[80] |
| Observed dose in supplements | 7.7 mg (Super Aytinal, Walgreens, 1998)<br>20 mg in 4 tabl. (TVM-49, Life Plus, 1998)<br>99 mg (Super Vite, VitaminPower, 1998). |
| Dietary source | leafy vegetables, fruit, meat. |
| Function | nerve transmission, muscle contraction. |
| Deficiency symptoms | marginal potassium deficiency impaired neuromuscular functions and reduced reflexes. |

*Table 18: iron*

| iron | (*ferrous sulfate*, ferrous gluconate, ferrous sulfate) |
|---|---|
| Minimum requirement | men: 1 mg<br>women: 2 mg[49] |
| Recommended daily allowance (RDA) | M: 9 mg<br>F: 15 mg<br>Note: the RDA value proposed for pregnant women by the Food and Nutrition Board of the US National Research Council is 30 mg Fe per day.[84] |
| Toxic dose | acute toxicity: nearly always due to accidental ingestion of iron-containing medicines and most often occurs in children. Severe toxicity occurs after the ingestion of more than 0.5 g of iron or 2.5 g of ferrous sulfate.[5]<br><br>chronic toxicity: excessive accumulation of body iron not only can result in excessive iron stores, but also can damage various organs (liver, pancreas, heart). Clinical manifestations appear when total body iron accumulation reaches 20-40 g (about 10x normal). A maximum safe daily intake is set at 75 mg.[86]<br><br>A high intake of iron or an iron excess (as in hemachromatosis) together with a high intake of vitamin C can lead to a conversion of harmless $Fe^{3+}$ to catalytic $Fe^{2+}$ which generates billions of free radicals. Over 10% of nonblacks and up to 30% of blacks have a gene for iron overload.[3]<br><br>The precise threshold for adverse effects of supplemental iron is not known but is probably also dependent on intakes of other minerals, e.g. manganese, zinc and protein.[43] |
| Observed dose in supplements | 1.0 mg (Davitamon Total, 1996)<br>3.6 mg (Supradyn Complex Forte, Roche, 1996)<br>20 mg (Liver plus Iron, Life Plus, 1998)<br>25 mg (Super Aytinal, Walgreens Co., 1998). |
| Dietary source | potatoes, bread, fruits, vegetables, meat. |
| Function | important for formation of hemoglobin, myoglobin and other substances such as the cytochromes, cytochrome oxidase, peroxidase and catalase.[49] |
| Deficiency symptoms | anemia, fatigue, anorexia, decreased gastric acid production.[4] |

*Table 19: zinc*

| | |
|---|---|
| zinc | (*zinc oxide*, zinc methionine, zinc gluconate, zinc chelate, zinc picolinate, zinc aspartate) |
| Minimum requirement | adults (general):<br>2.2 mg (World Health Organization, 1973)<br>5.2-7.6 mg (Nutrition Council of the Netherlands, 1992). |
| Recommended daily allowance (RDA) | M:10 mg<br>F: 9 mg<br>note: pregnant women, lactating mothers and children have higher minimum requirements and higher RDAs. |
| Toxic dose | Various cases of fever brought about by the inhalation of metal vapours have been reported. When administred orally in large quantities (450 mg), zinc induces vomiting. The toxic effects of chronic exposure to zinc are probably due largely to copper deficiency, since zinc displaces the copper contained in enzymes. The administration of 300 mg of zinc a day for six weeks has been found to adversely affect various immune system indicators.[50] Festa et al.[51] observed reduced copper absorption in subjects taking in about 20 mg of zinc a day.<br>The World Health Organization (WHO) recommends a limit of 45 mg of zinc a day for adults. The European Commission (EC) endorses the WHO's reasoning, but applies a different safety factor in its calculations, on the basis of which it suggests limiting zinc intake to 30 mg a day. The now defunct Nutrition Council suggested that zinc intake should not exceed 150 mg a day. The Committee on the Risk Evaluation of Substances endorses the European Commission's recommendation that zinc intake should not exceed 30 mg a day, but the Committee suggest that, where copper intake is low, zinc intake should be limited to a level below that advised by the EC.<br>Generally speaking, toxic effects are unlikely if zinc intake does not exceed 20 mg a day. |
| Observed dose in supplements | 3 mg (Davitamon Total, 1996)<br>15 mg in 4 tabl. (Ultra Minerals, VirtuVites, 1998). |
| Dietary source | lean meat, cheese, cereals, bread, nuts, seafoods (lobster, crab, oyster). |
| Function | integral part of many enzymes (carbonic anhydrase, lactic dehydrogenase, superoxide dismutase), component part of some peptidases and therefore is important for digestion of proteins in the gastrointestinal tract.[49] |
| Deficiency symptoms | dermatitis, diarrhoea, eye problems, psychological abnormalities and increased susceptibility to infection, night blindness.[4,52] |

# Appendix IV Trace elements

*Table 20: copper*

| copper | (*copper gluconate*) |
|---|---|
| Minimum requirement | not known.[4]<br>between 1.0 and 1.25 mg Cu/d is needed by adults for copper maintenance for periods up to 6 mo.[53] |
| Recommended daily allowance (RDA) | M: 1.5-3.5 mg<br>F: 1.5-3.5 mg |
| Toxic dose | At an intake of 10-15 mg, acute symptoms occur. Ingestion of larger amounts of oral copper salts may even produce death.[5]<br>There are limited data concerning the chronic toxicity of copper in experimental animals.[54] |
| Observed dose in supplements | 0.4 mg (Super-Vite, Vitamin Power, 1998)<br>1 mg in 4 tabl. (TVM-49, Life Plus, 1998)<br>1.5 mg in 3 tabl. (Support Tabs, Life Plus, 1998). |
| Dietary source | shellfish, organ meats, dried fruits, legumes, nuts. |
| Function | connective tissue development, myelination, necessary for Fe absorption and mobilization, needed by some oxidative enzymes. |
| Deficiency symptoms | hypochromic, microcytic anemia (defective hemoglobin synthesis) diarrhea, osteoporosis, nerve disorders.[4] |

*Table 21: cobalt*

| | |
|---|---|
| cobalt | mineral constituent of cobalamin (vitamin B12) |
| Minimum requirement | - |
| Recommended daily allowance (RDA) | - |
| Toxic dose | high levels of chronic oral administration may result in the production of goiter. The goitrogenic effect has been elicited by the oral administration of 3 to 4 mg/kg to children in the course of sickle cell anemia therapy.[5] |
| Observed dose in supplements | 50 µg (Super Aytinal, Walgreens Co., 1998) |
| Dietary source | liver, kidneys, sea vegetables, milk, oysters. |
| Function | essential as a component of vitamin B12, required for the production of red blood cells and prevention of pernicious anemia.[5] |
| Deficiency symptoms | dietary deficiency is uncommon, usually found in alcoholics, strict vegetarians, and pregnant or nursing women. The deficiency more often stems from an inability to absorb rather than a lack of the substance. Signs of a deficiency are: sore tongue, weight loss, body odor, back pains and tingling arms and legs.[55] |

*Table 22: iodine*

| iodine | (*potassium iodine*) |
|---|---|
| Minimum requirement | when the mean value of iodine in urine is less than 5 µg/dl, there is a risk of iodine deficiency disorders.[20] |
| Recommended daily allowance (RDA) | 40-120 µg for children up to age 10 (USA).[22]<br>150 µg for adults (USA).[22]<br>Note: optimal level of iodine in the diet is probably about 150 µg.[20] |
| Toxic dose | the human subject, not deficient in iodine, is remarkably tolerant of high levels of iodine intake because of a balanced system. Many patients have used it in gram amounts daily for treatments (as in asthma)[20]<br>The maximum safe daily intake is 700 µg.[80] |
| Observed dose in supplements | 150 µg (Super Aytinal, Walgreens Co., 1998)<br>Note: iodine is a constituent of many medications, such as vitamin tablets or capsules.[20] |
| Dietary source | the content of foods of both animal and vegetable origin are related to the soil on which they are grown. |
| Function | essential component of the thyroid hormones. Thyroid hormone is essential to development. |
| Deficiency symptoms | growth of the thyroid gland (goiter), reduced fertility, cretinism<br>deficiency during fetal development: growth retardation, damaged neuromuscular and cognitive attainment.[20] |

*Table 23: fluoride*

| fluoride | |
|---|---|
| Minimum requirement | - |
| Recommended daily allowance (RDA) | on the basis of empirical evidence, it appears that 0.05-0.07 mg/kg body weight per day is a fair estimate of the optimal dose.[56] For an adult, estimates of daily fluoride intake from food and beverages range from 1-3 mg/day.[20]<br><br>no dutch recommendations.[57] |
| Toxic dose | acute toxicity: the probably toxic dose is 5 mg fluoride/kg of body weight. The safely tolerated dose has been estimated to be 3-5 mg fluoride/kg.<br>chronic toxicity: the only known adverse effect associated with chronic ingestion of relatively low lowels of fluoride (1-2 mg/L in drinking water; optimally fluoridated water: 0.7-1.2 mg/L) is dental fluorosis (hypomineralization of enamel).[20] |
| Observed dose in supplements | 40 µg (Davitamon Total, 1998)<br>2.5 mg (NEW-TON, Sandripo S.A., Bruxelles, 1998). |
| Dietary source | the major influence on total fluoride intake is probably the fluoride content of drinking water. Processed products with chicken, fish and seafood products may also contain high levels of fluoride. Children may ingest fluoride from therapeutic fluoride products such as toothpaste and fluoride supplements. Other dietary sources include: seafood (especially sardines and salmon), cheese, meat and tea.[58] |
| Function | stimulates bone formation by osteoblastic stimulation, increases spinal bone density[59], prevention of tooth decay.[20] |
| Deficiency symptoms | tooth decay. |

*Table 24: chromium*

| chromium | (*chromium polynicotinate*, chromium chloride, chromium picolinate) |
|---|---|
| Minimum requirement | - |
| Recommended daily allowance (RDA) | 50 - 200 µg adults (USA).[22]<br>estimates of daily intake from food by humans are under 100 µg.[5] |
| Toxic dose | trivalent chromium has such a low order of toxicity that deleterious effects from excessive intake of this form of chromium do not occur readily. Trivalent chromium becomes toxic only at extremely high amounts.- chromium then acts as a gastric irritant rather than as a toxic element interfering with essential metabolism or biochemistry.[60] The trivalent form is the more common form, although the hexavalent form may be more toxic. The major effect from ingestion of high levels of chromium is acute tubular and glomerular damage. Evidence of kidney damage from lower level chronic exposure is equivocal.[5]<br>The safety of 200 µg chromium supplements given as chromium chloride has been established in a number of studies.[61] |
| Observed dose in supplements | 100 µg (Ultra Minerals, VirtuVites, 1998)<br>200 µg (Chromemate (niacin-bound chromium), Vitamin Power, 1998) *. |
| Dietary source | organ meats, mushrooms, broccoli, wheat germ. |
| Function | cofactor for insulin action, facilitating the attachment of insulin to the insulin receptors. |
| Deficiency symptoms | reduced insulin requirement, glucose intolerance, weight loss, peripheral neuropathy.[20] |

*Table 25: molybdenum*

| molybdenum | (*molybdeen chelate*) |
|---|---|
| Minimum requirement | minimum requirement requirement of healthy young men appears to be slightly >22 µg/day.[62] |
| Recommended daily allowance (RDA) | 75-250 µg (USA).[22] |
| Toxic dose | molybdenum is a relatively nontoxic element, in non-ruminants an intake of 100-5000 mg/kg of food or water is required to produce clinical toxicity symptoms.[62]<br>>1500 mg/24 h.[63] |
| Observed dose in supplements | 50 µg (Super Aytinal, Walgreens Co., 1998) |
| Dietary source | liver, whole grains, beans, milk and milk products, cereals. |
| Function | involved in metabolism of purines and pyrmidins. |
| Deficiency symptoms | hypermethioninemia, increased urinary xanthine and decreased urate excretion, severe brain damage, mental retardation.[20] |

*Table 26: selenium*

| selenium | (*L-selenomethionine*:*Se-rich yeast)* |
|---|---|
| Minimum requirement | 70 µg appears to be required to maintain Se balance for the standard human (70 kg body weight). The critical level for prevention of deficiency is 20 µg Se.[5] |
| Recommended daily allowance (RDA) | M: 50-150 µg<br>F: 50-150 µg<br>USA: 55 µg for women, 70 µg for men.[22] |
| Toxic dose | early symptoms of selenium are fatigue and gastrointestinal disturbances and toxicity appear at an intake of 200 µg.[4,5,43,80] Nail and hair abnormalities and other toxic effects occur at doses over 6 times the RDA.[35]<br>One study in China reports toxicity at doses higher than 1600 µg.[56] |
| Observed dose in supplements | 35 µg (Davitamon Total, 1996)<br>100 µg (Selenomax Complex, Nutraceutix: BioPower, 1998) *<br>200 µg (Selenomax Complex, Nutraceutix: BioPower, 1998) * |
| Dietary source | vegetable products[4](content depends on natural selenium contents of food and water), brazil nuts, crab, beef kidney. |
| Function | as an antioxidant closely linked to vitamin E, involved in prostaglandin synthesis and essential amino acid metabolism, maintaining glutathion homeostasis, necessary for normal male fertility, essential for metabolism of the thyroid gland, believed to play a role in the immune system and the body's response to infection.[64] |
| Deficiency symptoms | pancreatic degeneration, cardiomypathy.[65] |

# Appendix V Hormones

*Table 27: melatonin*

| | |
|---|---|
| melatonin | N-acetyl-5-methoxy-tryptamine |
| Minimum requirement | - |
| Recommended daily allowance (RDA) | - |
| Toxic dose | there currently is a total lack of information on the toxicology of melatonin.[66] In subjects taking melatonin, no evidence of toxicity in a strictly sense has been reported (i.e. no deaths or serious accidents) but adverse side effects such as gastrointestinal disorder, hypotension, headaches and nightmares are reported. Five gram of melatonin given daily for 4 weeks 5 h before the mean time of sleep onset significantly advanced both sleep and wake onset.[66] Short-term use of low doses of melatonin appears safe, but there is no information on its long-term side effects or interactions with drugs or other antioxidants.[31]<br>Note: in the USA it is sold over the counter but in Europe it's not because it is considered a 'neurohormone'. In the Netherlands, a dose of 100 µg per supplement is allowed. |
| Observed dose in supplements | 300 µg synthetic melatonin (Melatonin Central, Worldwide Labs', 1998)<br>1.0 mg synthetic melatonin (Melatonin, Qlife, 1998)<br>3.0 mg synthetic melatonin (Melatonin Central, Worldwide Labs', 1998).<br>Note: an inappropriate time schedule of melatonin dosing could have long term deleterious effects.[66] |
| Dietary source | our diet supplies little if any melatonin. The amino acid tryptophan increases endogenous production of serotonin, which is a precursor for melatonin. Thus, diets rich in tryptophan may affect indirectly the production of melatonin.[31] |
| Function | secreted by the pineal gland, antioxidant, immunoprotective and it plays an important role in circadian and annual biological rhythms.[31,66] |
| Deficiency symptoms | - |

*Table 28: DHEA*

| DHEA | dehydroepiandrosterone |
|---|---|
| Minimum requirement | - |
| Recommended daily allowance (RDA) | Note: there is no convincing evidence that DHEA has any beneficial effect on aging or any disease.[67] |
| Toxic dose | various androgenic effects, including acne, hair loss, hirsutism and deepening of the voice have been reported with use of DHEA in women (the latter two effects may be irreversible). The effect of DHEA on the tumors of prostate, breast and endometrium are unknown (stimulated by androgens and estrogens).[67] In one study in which subjects aged 40-70 y received 50 mg of DHEA daily, serum levels of DHEA were restored to the level found in young adults and serum levels of insulin like growth factor increased in both sexes.[68] Whether DHEA has any effect on body composition, fat distribution, serum lipid levels or insulin sensitivity is unclear.[69] |
| Observed dose in supplements | 25 mg. DHEA (sustained release, Worldwide Labs', 1998) *<br>50 mg. DHEA (DHEA, Manna Nutrition, 1998) *. |
| Dietary source | - |
| Function | DHEA is a steroid precursor of both androgens and estrogens and is secreted by the adrenal cortex, especially during fetal life. Plasma concentrations of DHEA and its metabolite (DHEA sulfate) peak at about 20 years and then decrease progressively with age.[67] |
| Deficiency symptoms | during fetal life: incomplete development of the male sex organs.[49] |

# Appendix VI Fatty acids

*Table 29: omega-6 fatty acids*

| Omega-6 fatty acids | (*linoleic acid (LA); gamma linoleic acid (GLA); arachidonic acid (AA)*) |
|---|---|
| Minimum requirement | In the omega-6 family of fatty acids, linoleic acid (LA) is the major essential fatty acid and no more than 1-2% of calories is required to relieve symptoms of essential fatty acid deficiency[89] |
| Recommended daily allowance (RDA) | LA is an essential fatty acid, so it must be included in the diet. The recommended intake is about 3-5% of dietary energy.[20, 89]<br>Note:<br>The typical North American diets provide 7% of energy as linoleic acid.[70]<br>GLA and AA are synthesized from LA<br>AA: no mammalian species has yet been found to require dietary AA.[20] |
| Toxic dose | - |
| Observed dose in supplements | LA: 1000 mg (Tonalin, Mineral Connection, 1998) *<br>LA: 1020 mg (Essential Balance, Omega Nutrition, 1998)<br>GLA: 15mg (Omega 3 and Omega 6, Life Services, 1998)<br>GLA: 321 mg (Essential Balance, Omega Nutrition, 1998). |
| Dietary source | linoleic acid: vegetable oils (sunflower-, safflower-, corn-, soybean oil)<br>γ-linolenic acid: primrose oil, blackcurrent seed oils,<br>arachidonic acid: egg yolk, organ meats (liver) |
| Function | in general, the composition of the fatty acids in the diet determines partly the fatty acid composition of membrane phospholipids. As a result, dietary fat composition can influence several membrane-related functions, such as hormone binding and associated enzyme and transporter activities. Enzymatic metabolism of omega-6 fatty acids produces eicosanoids. These eicosanoids are important and potent mediators of many biochemical processes and play a critical role in the coordinating physiological interactions among cells (for example: essential for normal dermal integrity). Other specific roles for various n-6 fatty acids are still being discovered.[20] |
| Deficiency symptoms | Few cases of essential fatty acid deficiency (EFD) have been observed. Symptoms of EFD are: scaly dermatitis, fatty degeneration of the liver, anemia and thrombocytopenia.[20] |

*Table 30: omega-3 fatty acids*

| | |
|---|---|
| Omega-3 fatty acids | *(eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α- linolenic acid (ALA))* |
| Minimum requirement | 0,5 % ALA of calories avoids any apparent deficiency symptoms[20] |
| Recommended daily allowance (RDA) | ALA is an essential fatty acid, i.e. must be present in the diet. A dietary intake of 0.5-1.0% ALA of energy gives maximum tissue levels of DHA. [20, 89] EPA and DHA are synthesized from ALA. The optimal requirement for EPA and DHA is around 0.4% of calories[89]<br>Note: omega-3 and omega-6 fatty acids compete for the same desaturase enzymes (metabolic conversion of fatty acids). For example, high intakes of LA (omega-6) with low intakes of ALA could result in competitive pressure against omega-3 fatty acids.[20] A general agreement is that intake of omega-6 and omega-3 essential fatty acids ranging from 4:1 to 6:1 is prudent.[89] |
| Toxic dose | - |
| Observed dose in supplements | 60 mg EPA and 40 mg DHA caps.(Omega 3 & Omega 6, Life Services, 1998)<br>720 mg EPA and 480 mg DHA in 2 caps. (Super Epa Fish Oil Concentrate, Wholesale Distribution Center, Vitanet, 1998)<br>ALA: 1020 mg (Essential Balance, Omega Nutrition, 1998)<br>ALA: 5872 mg (The Total EFA, Netrition, 1998). |
| Dietary source | linolenic acid: soybean-, linseed-, canola oils<br>longer chain n-3 fatty acids: high fat fish |
| Function | precursors for formation of eicosanoids and they have specific roles in a variety of normal physiological processes (for example maintaining the fluidity of cell membranes, particularly in the retina and brain). No essential metabolic role for ALA, other than a precursor for synthesis of EPA and DHA has yet been identified.[20] |
| Deficiency symptoms | few cases of essential fatty acid deficiency have been observed. Symptoms are: scaly dermatitis, fatty degeneration of the liver, anemia and thrombocytopenia.[20] |

# Appendix VII Associated nutritional factors

*Table 31: quercetin*

| | |
|---|---|
| quercetin | quercetin is a flavonoid<br>*(quercetin)* |
| Minimum requirement | - |
| Recommended daily allowance (RDA) | it has been estimated that the average daily intake of flavonoids for Americans is approximately one gram.[71]<br>On the basis of recent studies, a normal diet contains 23-34 mg flavonoids on average; the majority of this is quercetin.[72]<br>The actual intake of quercetin in the Netherlands is 16 mg.[73] |
| Toxic dose | - |
| Observed dose in supplements | 300 mg (Quercetin 300, Allergy Research Group, 1998) *. |
| Dietary source | the outer layers of fruits and vegetables: berries, tomatoes, potatoes, broad beans, peapods, onions with colored, nuts, seeds.[71] |
| Function | exhibits antioxidant and free radical-scavenging properties (scavenges superoxide anion, singlet oxygen and lipid peroxy radicals in vitro).[74] |
| Deficiency symptoms | - |

*Table 32: lipoic acid*

| lipoic acid | *(alpha lipoic acid)* |
|---|---|
| Minimum requirement | animals are fully capable of lipoic acid biosynthesis and it has not been shown to be essential as a dietary component for man.[27] |
| Recommended daily allowance (RDA) | - |
| Toxic dose | lipoic acid supplements to purified diets of chicks, rats and turkey poults has been without toxic effect.[26] |
| Observed dose in supplements | 600 mg in 3 caps. (Alpha Lipoic Acid, Twinlab, 1998) *. |
| Dietary source | - |
| Function | essential cofactor in metabolic reactions involved in energy utilization, stimulates glucose transport and has a positive effect on insulin-stimulated glucose uptake. It may also have effects on genes and regulatory proteins involved in normal growth and metabolism. Lipoic acid and its reduced form, dihydrolipoic acid, are effective as both fat-soluble and water-soluble antioxidants.[31] |
| Deficiency symptoms | none reported.[26] |

*Table 33: choline*

| choline | (*choline bitartrate*) |
|---|---|
| Minimum requirement | adequate intake (for prevention of liver damage as assessed by measuring serum alanine aminotransferase levels):<br>M: 550 mg (USA)[23]<br>F: 425 mg (USA)[23] |
| Recommended daily allowance (RDA) | - |
| Toxic dose | the toxicity appears to be very low. However, deleterious effects have been reported for the salt choline chloride; these have included growth depression, impaired utilization of vitamin B6 and increased mortality. It is not clear whether the apparent toxicity of that form of the vitamin have been due to the perturbation of acid-base balance caused by the high level of chloride administered with large doses of the salt. In humans, high doses (e.g. 20 g) have produced dizziness, nausea and diarrhea.[26,27]<br>Critical adverse effects are hypotension with cholinergic side effects (e.g. sweating, diarrhea) and fish body odor. The tolerable upper intake level for adults is 3.5 g/d.[23] |
| Observed dose in supplements | 150 µg (Super Vite, VitaminPower, 1998)<br>250 mg (Trophic Choline, Supplements on-line, 1998) *. |
| Dietary source | egg yolk, glandular meats (e.g. liver, kidney, brain, soybean products, peanuts). All natural fats contain some choline; therefore, it is widely distributed in food.<br>Note: used as an ingredient or additive to many processed foods and food supplements because it is a good emulsifying agent and it is very stable.[26] |
| Function | structural element of biological membranes and promotes lipid transport (as phosphatidylcholine), neurotransmitter (acetylcholine), source of labile methyl groups (after conversion to betaine).[26] |
| Deficiency symptoms | clear cases of choline deficiency have not been reported in humans but this may only reflect the adequacy of other methyl donors. Possible signs of choline deficiency are a decreased growth, renal hemorrhage and perosis.[26] |

*Table 34: coenzyme Q-10*

| | |
|---|---|
| Co-Q-10 (ubidecarenone) | *(coenzyme Q10*: ubiquinone) |
| Minimum requirement | althoug dietary CoQ contributes to the pool of CoQ-10 in humans, the major part is synthesized (from tyrosine, phenylalanine and acetyl-CoA), primarily in the liver.[31] |
| Recommended daily allowance (RDA) | not known.[75]<br>it is not considered an essential nutrient, so there is no RDA.[31]<br>estimated average daily intake in the USA is about 3-5 mg.[31] |
| Toxic dose | major toxicity of coenzyme Q10 has not been described, but nausea and gastric pain and other adverse effects have been attributed to oral medication. The safety has not been fully or systematically evaluated.[31] |
| Observed dose in supplements | 30 mg Co-Q-10 (Co-Q-10+, Body Wise, 1998) *<br>50 mg Co-Q-10 (Co-Q-10-PLUS, Life Plus, 1998) *.<br>note: doses taken as supplements range considerably; common doses used as supplement are 10-30 mg/day.[31] |
| Dietary source | meats, fish, vegetable oils, spinach, broccoli, soy, wheat germ. |
| Function | operates in electron shuttling between the citric acid cycle and the respiratory chain, antioxidant.[20] |
| Deficiency symptoms | - |

*Table 35: carnitine*

| | |
|---|---|
| Carnitine | Note: carnitine is an amino acid, but it has no role in protein synthesis (6). (*acetyl-L-carnitine*) |
| Minimum requirement | - |
| Recommended daily allowance (RDA) | healthy adults can synthesize carnitine at rates sufficient for their needs. However, the total carnitine biosynthetic capacity may be immature in newborns.[26] |
| Toxic dose | - |
| Observed dose in supplements | 330 mg (Carnitor, Sigma-Tau Pharmaceuticals, Inc., 1998) *<br>1000 mg in 2 tabl. (Acetyl-L-Carnitine, Life Services, 1998) *. |
| Dietary source | red meats and dairy products, beef, lamb, chicken. |
| Function | carnitine functions as a carrier of fatty acyl CoA from the cytosol into the mitochondrial matrix for oxidation, so it's involved in lipid metabolism. |
| Deficiency symptoms | abnormally low circulating carnitine levels have been found in humans with severe protein malnutrition (nutritional deprivation of the precursors lysine or methionine) and in hemodialysis patients. Hyperlipidemia, cardiomyopathy, skeletal muscle asthenia and cramps.[26] |

*Table 36: inositol*

| inositol | (*inositol*) |
|---|---|
| Minimum requirement | it appears that, under certain conditions (e.g. situations in which the intestinal microflora is disturbed, high levels of fat in the diet) animals can have need for pre-formed myo-inositol.[26] |
| Recommended daily allowance (RDA) | mammals can synthesize myo-inositol *de novo* ultimately from glucose; biosynthetic capacity has been found in the kidney ( ± 2 g/kidney/day) and other tissues in humans.[26] |
| Toxic dose | - |
| Observed dose in supplements | 90 µg (Ultra Potency Multiple 90, Vitamin Power Company, 1998)<br>650 mg tabl. (Inositol, Country Life, 1998) *. |
| Dietary source | seeds of plants (e.g. beans, grains and nuts), organ meats. |
| Function | affecter of the structure and function of membranes, source of arachidonic acid, mediator of cellular responses. |
| Deficiency symptoms | deficiencies in humans are not known/not reported. In fish: anorexia, edema, anemia, reduced growth, impaired efficiency of feed utilization.[26] |

*Table 37: creatine*

| creatine | (*creatine monohydrate*, creatine phosphate (also called phosphocreatine)) |
|---|---|
| Minimum requirement | - |
| Recommended daily allowance (RDA) | - |
| Toxic dose | - |
| Observed dose in supplements | 5000 mg in 10 caps. (Universal Gro-Pro, Professional Supplements, 1998)*<br>note: powders are more common/popular than capsules. |
| Dietary source | - |
| Function | creatine and phosphate can combine and yield a high energy phosphate bond. When it decomposes, it provides large amounts of energy for ATP reconstitution.[49] So, in general, it's crucial for energy flow within skeletal muscle. Creatine is synthesized from glycine, arginine and a suitable source of methyl groups.[20] |
| Deficiency symptoms | - |

*Table 38: glucosamine*

| | |
|---|---|
| glucosamine | combination of glutamine and glucose<br>(*glucosamine sulfate*, glucosamine HCL, N-acetyl-glucosamine) |
| Minimum requirement | glutamine is a dispensable (nonessential) amino acid, it can be synthesized by mammals via transamination reactions. |
| Recommended daily allowance | - |
| Toxic dose | - |
| Observed dose in supplements | 500 mg in 2 caps (Glucosamine Relief, IPS Inc., 1998)<br>1500 mg in 3 caps (Glucosamine Sulfate, Allergy Research Group, 1998) *. |
| Dietary source | glucose: fruits and vegetables<br>glutamine: protein rich foods |
| Function | glutamine appears to play a specific role in maintaining function of rapidly proliferating cells such as lymphocytes and mucosal enterocytes. Glutamine is considered a conditionally essential amino acid in times of stress.[20] Glucose is a monosaccharide and is the primary fuel used by most of the cells, but it is the principal fuel for the central nervous system. |
| Deficiency symptoms | - |

*Table 39: lycopene*

| | |
|---|---|
| lycopene | lycopene is a carotenoid<br>*(lycopene)* |
| Minimum requirement | - |
| Recommended daily allowance (RDA) | daily intake varies from 0.8 mg (Finland) to 3.7 mg (USA). |
| Toxic dose | - |
| Observed dose in supplements | 10 mg (Lycopene 10MG, Twinlab, 1998) *. |
| Dietary source | tomatoes and tomato products (juice, paste, sauce), water melon. |
| Function | among the common dietary carotenoids, lycopene has the highest singlet oxygen quenching capacity in vitro. It may be one of the protective factors in fruit and vegetable diets.[76] Other biological activities include induction of cell-cell communication and growth control (but no provitamin A activity).[77] |
| Deficiency symptoms | - |

*Table 40: ß-carotene*

| ß-carotene | |
|---|---|
| Minimum requirement | - |
| Recommended daily allowance (RDA) | 2 mg.[6]<br>the desirable intake of ß-carotene is 3 mg (necessary to achieve a particular plasma concentration, associated with reduced cardiovascular disease).[78]<br>The actual intake in the Netherlands is 2-3 mg[73], in the USA 3 mg.[31] |
| Toxic dose | at a high intake of ß-carotene, the conversion of the provitamins A in the gut is very inefficient. An other protective mechanism against hypervitaminosis is the unidirectional oxidation of the vitamin to a form (retinoic acid) that is rapidly catabolized and excreted.[26]<br>Hypercarotenemia (yellowing of the skin, reversible) may occur in individuals taking supplements of >30 mg/d for extended periods.[6]<br>In two large intervention studies, a prolonged dose of ß-carotene (20-30 mg/day) increased the mortality due to ischemic heart disease and lung cancer in smokers compared to smokers who did not receive ß-carotene supplementation.[7,8] Maybe in early stages of the cancer process, the beneficial effects of ß-carotene are most evident whereas at an advanced stage it may have detrimental effects.[6] |
| Observed dose in supplements | 15 mg (=25,000 IU of vitamin A activity) (Beta Carotene, Life Extension, 1998) *<br>19.8 mg (=33,000 IU of vitamin A activity) (BetaMax Carotene +, Life Services, 1998) *. |
| Dietary source | green leafy vegetables (broccoli, spinach), carrots, orange colored fruits, sweet potatoes, red palm oil.[39] |
| Function | ß-carotene is one of the few carotenoids that has provitamin A activity and is the carotenoid that is most efficiently converted to retinol in the human body.[39] It is also an efficient quencher of singlet oxygen and can directly scavenge free radicals.[79] ß-carotene may enhance immunological function.[39] |
| Deficiency symptoms | - |