chapter twelve

Adverse effects of nutrients

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12.1 Introduction to the toxicological aspects of nutrient intake

This chapter focuses on the toxicological aspects of a special group of substances, the nutrients. With respect to nutrient intake two points are of high toxicological importance.

First, attention should be paid to the margin between physiological need and toxic intake, i.e., dose. On the one hand, nutrients are necessary for life and good health, on the other, they may pose life threatening risks. When the intake of nutrients is very low, this may lead to lethal deficiencies, whereas a very high intake may cause toxic effects. The requirements for optimal nutrient intake are based on both deficiency and toxicity data. The optimal intake of a nutrient may be defined as the intake that meets the minimal physiological needs of an organism for that nutrient, and does not cause adverse effects. An example of the implications of overintake is the acute vitamin A toxicity in Arctic and Antarctic explorers on the consumption of polar bear liver containing about 600 mg retinol per 100 g liver. The explorers were informed by the Eskimos that eating polar bear liver may cause drowsiness, headache, vomiting, and extensive peeling of the skin.

A second point that deserves attention with respect to nutrients is the possible interaction between components of a diet. If there is an interaction, there is no adequate procedure to evaluate the toxicological safety, since the traditional procedure for the evaluation of toxicological safety is inappropriate. For example, if a meal consists of protein-rich fish or fish products, and green leafy vegetables, like spinach, interaction may occur leading to the formation of nitrosamines (e.g., dimethylnitrosamine) in the stomach. Dimethylnitrosamine has been shown to induce tumors in experimental animals.

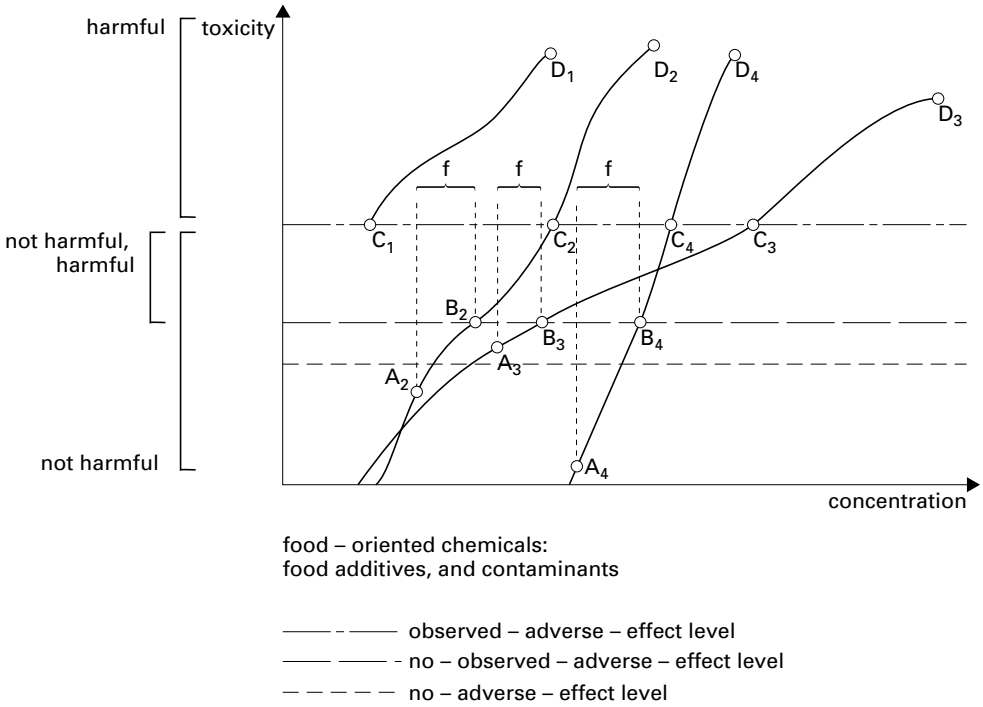

Figure 12.1 Impact of concentration on health in the case of food-oriented substances, such as food additives and contaminants. A, no-observed-adverse-effect concentration (acceptable daily intake, ADI); B, no-observed-adverse-effect level (NOAEL); C, minimum-observed-adverse-effect level; D, lethally high concentration; C_1–D_1, genotoxic substances such as nitrosamines; A_2–D_2, food contaminants such as nitrite; A_3–D_3, food additives such as benzoic acid; A_4–D_4, toxins of microbial origin such as botulinum toxin; f, safety margin.

The actual toxicological risks associated with the intake of excessive amounts of nutrients differ from nutrient to nutrient. For instance, induction of toxic effects is hard to imagine after vitamin C intake, while vitamin A poisoning following the consumption of livers of animals high in the food chain, as in the example described above, is well-known. If common nutrients pose health hazards, they must be either highly active or accumulate to a high degree in tissues. In order to gain more insight into the toxicological aspects of nutrient intake, it is useful to divide food chemicals into two groups: food-oriented and body-oriented chemicals.

Food-oriented chemicals have no nutritional value and are primarily associated with food. The group of food-oriented chemicals includes food additives (preservatives such as benzoic acid), antioxidants (butylated hydroxyanisole, BHA), (sweeteners, such as sorbitol), food contaminants (nitrate and nitrite, lead and cadmium, polycyclic aromatic hydrocarbons), and natural toxins (aflatoxins). Assessment of the toxicological risks from the intake of food-oriented chemicals is based on the results of extensive, carefully regulated toxicological screening. Therefore, food-oriented chemicals are considered to be relatively safe (see Figure 12.1). The toxicology of these substances is discussed in Chapters 9, 10, and 11 in more detail.

Body-oriented food chemicals are the nutrients. Nutrients are necessary for growth, maintenance, and reproduction of living organisms (body-oriented). They are divided into two groups: macronutrients (fats, carbohydrates, and proteins) and micronutrients (vitamins and minerals, including trace elements).

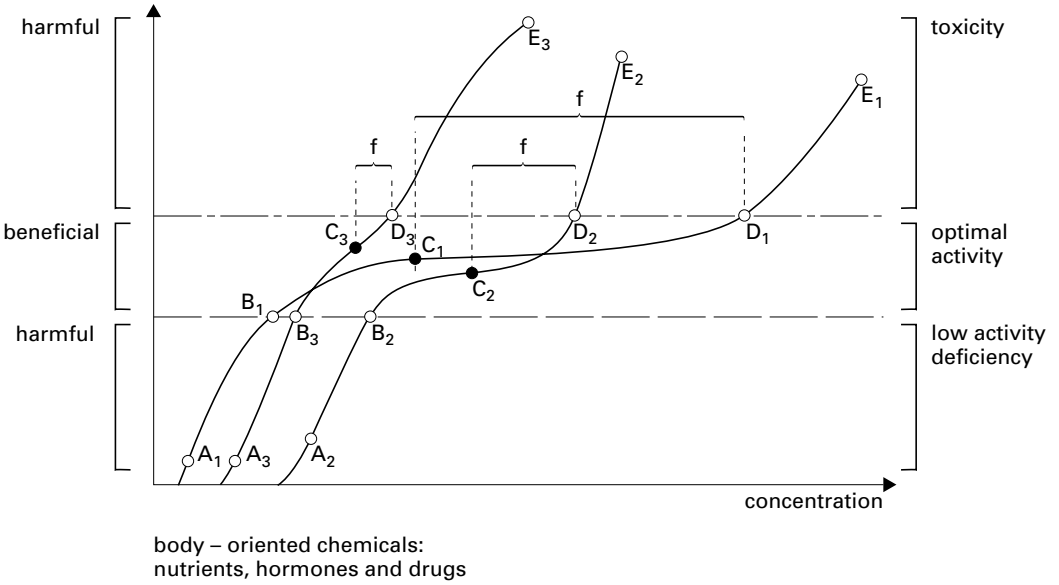

Figure 12.2 Impact of concentration on health in the case of body-oriented substances, such as nutrients, hormones and drugs. A, lethally low concentration; B, minimum concentration compatible with good health; C, concentration for optimal health (nutrients; Recommended Dietary Allowance, RDA); D, maximum concentration compatible with good health; E, lethally high concentration. A_1–E_1, hydrophilic vitamins such as vitamin C and B_1; A_2–E_2, lipophilic vitamins such as vitamin A and E, or selenium; A_3–E_3, macronutrients such as fat; f, safety margin.

For the intake of nutrients recommended dietary allowances (RDAs) are set by official committees. RDAs are defined as the intake levels of essential nutrients that (on the basis of present scientific knowledge) meet the needs of practically all healthy persons. Generally, these levels are considered to be safe (see Figure 12.2 and Table 12.1).

In the next sections, the present knowledge of the toxicity and safety of a number of selected nutrients are discussed. A more extensive study of nutritional toxicology is beyond the scope of this textbook. (For information about nutrients that are not discussed here see the reference list).

12.2 Macronutrients

For a good understanding of the toxicological aspects of the intake of macronutrients, it is important to know that the dietary levels of the three categories of macronutritients are closely related to each other. All three are sources of energy. If the energy intake percentage of one of the macronutrients changes, this will inevitably affect the intake percentage of another. This is shown in Figure 12.3. Official committees recommend a dietary protein intake of 7% of the total energy intake (E), a fat intake of about 30 to 35 energy% and a carbohydrate intake of about 60 energy% (see Figure 12.3a). In the Western countries, the estimated average intake of protein is 15 energy%, of fat, about 40%, and of carbohydrate, about 45 energy% (see Figure 12.3b).

12.2.1 Fats

A twofold increase in dietary fat intake will result in the consumption of about 80 energy% of lipid without a significant intake of carbohydrate (see Figure 12.3c). A large number of

Table 12.1 Recommended dietary allowances (RDAs), minimum-observed-adverse-effect levels and safety margins for various macronutrients and micronutrients

Nutrient	Unit	Recommended dietary allowance[1]	Minimum-observed-adverse-effect level	Safety margin
Macronutrients				
Fat	energy%	35	50	1.4
Carbohydrate	energy%	60	90	1.5
Protein	energy%	7	30	4.3
Micronutrients				
Vitamins				
Lipophilic				
Vitamin A	µg	1000	15,000	15
Vitamin D	µg	10	50	5
Vitamin E	mg	10	>900	>80
Hydrophilic				
Vitamin C	mg	60	>12,000	>200
Nicotinic acid	mg	20	1000	50
Thiamin	mg	1.5	>500	>300
Vitamin B_6	mg	2	2000	1000
Vitamin B_{12}	µg	2	>100	>50
Biotin	µg	100	>10,000	>100
Minerals				
Iron	mg	10	180	18
Sodium	mg	500	2500	5
Potassium	mg	2000	18,000	9
Calcium	mg	800	>2500	>3
Trace elements				
Iodine	µg	150	>2000	>130
Zinc	mg	15	150	10
Selenium	µg	150	5000	33
Fluorine	mg	1	10	10
Copper	mg	3	>35	>13
Manganese	mg	5	10	2
Molybdenum	µg	250	10,000	40

[1] The allowances are expressed in terms of average daily intake over time for adults.

studies showed that dietary intake levels of fats, ranging from 40 to 50% of the total energy intake, already lead to a variety of adverse if not toxic effects.

The higher incidence of cancer (of epithelial origin, e.g., breast cancer, Figure 12.4) is well-known. When the total intake of fat is low, polyunsaturated fats appear to be more effective than saturated fats in carcinogenesis. The role of fat in carcinogenesis may be ascribed to tumor promotion. Lipid peroxidation (see Part 1, Chapter 6 and Part 2, Chapter 9) products have been reported to cause cell proliferation. Lipid peroxidation may also be involved in the induction of toxic effects in a number of other ways.

The formation of products such as hydroperoxides and unsaturated aldehydes (e.g., hydroxynonenal) may cause toxic interactions at various levels. Not only membranes and enzymes appear to be primary targets, but also DNA. Hydroxynonenal as well as hydroxyl radicals — formed by metal ion-catalyzed reduction of hydroperoxides — may form DNA-adducts (see Part 2, Chapter 9).

If lipid peroxidation results in excessive consumption of reducing equivalents, oxidative stress may occur. Oxidative stress may lead to the disturbance of homeostases, viz.

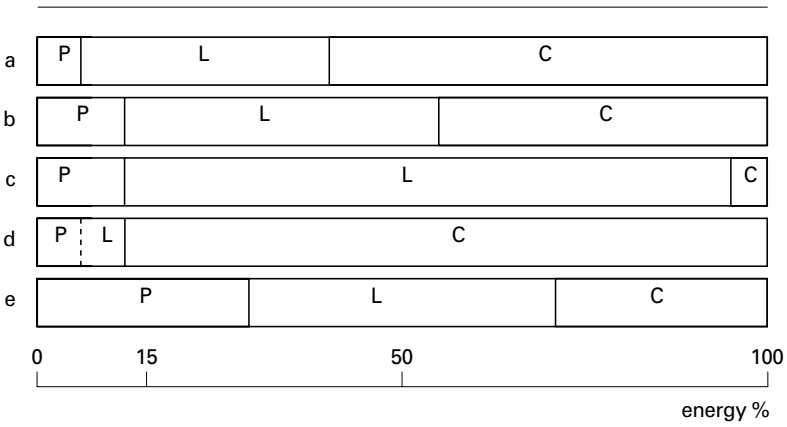

Figure 12.3 Effect of changes in the lipid (L), carbohydrate (C) and protein (P) content of the diet on nutritional balance expressed in terms of energy percentage (energy%) of the total intake. a) Intake of macronutrients recommended by official committees (protein 7 energy%, lipid 30-35 energy%, carbohydrate 58–63 energy%); b) Estimated intake of macronutrients (protein 15 energy%, lipid 40 energy%, carbohydrate 45 energy%); c) Twofold increase in fat intake (protein 15 energy%, lipid 80 energy%, carbohydrate 5 energy%); d) Twofold increase in carbohydrate intake (protein 7 energy%, lipid 7 energy%, carbohydrate 86 energy%). e) Twofold increase in protein intake (protein 30 energy%, lipid 40 energy%, carbohydrate 30 energy%).

thiol homeostasis and Ca^{2+} homeostasis. Thiol groups are then oxidized, and as a result, thiol group-dependent enzymes, like enzymes mediating Ca^{2+} transport, are inactivated. Also, indirect effects may be associated with dietary fat intake. This may concern interactions between food components. Fat intake is known to affect both bioactivation and detoxication of substances. High-fat diets appeared to enhance tumor induction in rats treated with aflatoxin B1 and diethylnitrosamine. Activation of cytochrome P-450 isoenzymes is believed to be involved in the increase in tumor incidence by these chemical carcinogens. An example of an interaction on the detoxication level is the depletion of the antioxidant vitamin E after high intake of polyunsaturated fatty acids. Vitamin E provides protection against peroxidation in general, including that of fatty acids.

12.2.2 Carbohydrates

A twofold increase in carbohydrate intake will result in a considerable decrease in lipid and protein intake (see Figure 12.3d). The adverse effects after excessively high carbohydrate intake are attributed to decreased intakes of the other macronutrients, rather than to the toxicity of carbohydrates.

A high dietary intake of specific carbohydrates has been reported to affect the health of small groups of the population. The absence of disaccharidases in the brush border of the intestinal mucosa connected with genetic as well as contracted disorders gives rise to absorption disturbances and chronic diarrhea. Deficiencies of the disaccharidases sucrase and maltase are rare. On the other hand, lactase deficiency occurs rather frequently. Symptoms of lactose intolerance are usually mild or absent unless large quantities are taken, e.g., a liter of milk, which contains 50 g of lactose. The cause of lactase deficiency may be of three types. First, there is the rare congenital lactase deficiency, with symptoms showing shortly after birth. Secondly, there is a very common ethnic form which affects a large part of the human population. In Asians and many Africans, the enzyme activity disappears at varying ages between infancy and adultness. Lactase cannot be induced in

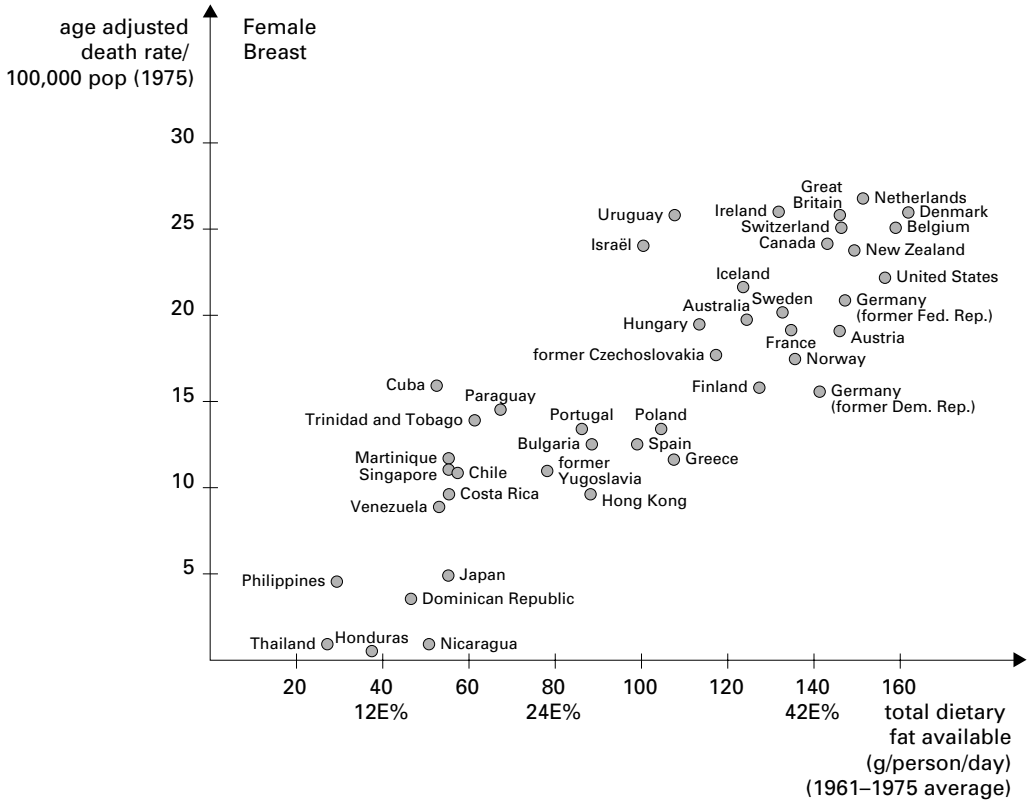

Figure 12.4 Relationship between age-adjusted mortality from breast cancer and total dietary fat available for consumption in different countries. Source: Carroll, 1980.

adults who have lost it. The frequency distribution of lactase deficiency in adults is believed to be the result of natural selection. The third cause of lactase deficiency is disease of the small intestine.

Lactase deficiency is an illustrative example of the importance of information on and education in toxicology. Many people cannot tolerate large quantities of milk or dairy products and hence, suffer from digestion disorders.

12.2.3 Proteins

A twofold increase in protein intake (30 energy%) (see Figure 12.3e) resulted in acceleration of the processes that lead to renal glomerular sclerosis. Further, it has been suggested that habitual high protein intake contributes to osteoporosis. However, protein intakes slightly higher than the physiological need are generally believed to be safe, because excess nitrogen is efficiently eliminated. This occurs mainly in the liver, where amino acids are metabolized to urea. Based on these findings, official committees recommend an upper limit of twice the RDA for protein. Oxidation of sulfur-containing amino acids has both nutritional and safety implications.

The nutritional value of proteins is determined by their amino acid composition, digestibility, and the utilization of absorbed amino acids originating from the proteins. The sulfur-containing amino acid content of many vegetables is low, particularly that of legumes. During processing and/or storage of food proteins, the sulfur-containing amino acids may be oxidized, resulting in a lower availability, i.e., in a reduction of the nutritional value.

The oxidized amino acids (e.g., lysinoalanine) have been shown to be toxic when large quantities of their free forms are consumed. Little is known about the mechanisms underlying the toxic effects of the oxidized sulfur-containing amino acids.

Protein intake may also indirectly lead to the induction of adverse effects. A well-known example of interactions between food components resulting in the formation of toxic products is nitrosamine formation. Secondary amines from fish protein may react with nitrite, originating from vegetable intake resulting in the formation of nitrosamines (for nitrosamine formation, see Part 2, Chapter 9). If vitamin C is also a component of the diet, the formation of nitrosamines can be prevented. Vitamin C inhibits the nitrosation reaction.

12.3 Micronutrients

12.3.1 Vitamins

For vitamins, health risks are traditionally associated with deficiencies. If a large intake range is considered, there is the risk of toxicity (see Figure 12.2). As far as the margin between physiological need and toxic dose is concerned, two groups of vitamins are distinguished: the lipophilic vitamins (vitamins A, D, E, and K) and the water-soluble vitamins (vitamin C, biotin, niacin, pantothenic acid, and folate, and the vitamins B). For the first group the margin may be relatively narrow, for the latter very wide.

Excessive vitamin intake can lead to a variety of toxic effects. In a number of cases, vitamin-induced toxicity is well-known. In other cases, vitamins are only slightly toxic or rather harmless. Although the vitamin content of the diet usually does not lead to toxic effects, it will be of increasing importance to take care of the standards set for vitamin intake in view of the recent trend of vitamin supplementation and fortification. In addition, vitamins are more and more used in processed food as naturally occurring antioxidants instead of synthetic antioxidants.

Also, long-term consumption of high doses of vitamins may be hazardous, even though they are rapidly eliminated. The lipophilic vitamins A and D pose the highest risk, as they can accumulate in the body.

12.3.1.1 Lipophilic vitamins

Vitamins are illustrative examples of body-oriented substances with their specific functions in organisms. It is mainly through the mechanisms underlying these functions that at high intake levels vitamins may be toxic to the organism (hypervitaminosis). Therefore, this section studies the toxicity of the lipophilic vitamins (A, D, E, and K) in relation to their intake, preceded by brief descriptions of their physiological functions.

Vitamin A represents a group of substances necessary for reproduction, cellular differentiation, and proliferation of epithelia, growth, integrity of the immune sytem, and normal eye sight. Retinal, formed from retinol, is involved in the so-called visual cycle. In this cycle, the retinal pigment rhodopsin (visual purple) is bleached on exposure to light. Next, a stimulus is sent to the rods in the retina. The bleaching of visual purple enables the human eye to see at night. In case of vitamin A deficiency, one of the symptoms is night blindness.

The large group of retinoids comprises naturally occurring substances with some vitamin A activity, such as retinol, retinaldehyde, and retinoic acid, and a large number of synthetic, structurally-related substances with or without vitamin A activity. In foods of animal origin, vitamin A is present as retinyl ester. The sources richest in vitamin A are fish liver oils. Further, considerable amounts are also present in fortified whole milk and eggs.

Food consumption data showed that the average daily dietary intake by adult men is about 1500 μg retinol equivalents (RE). The RDA for vitamin A is 1000 μg RE. If consumed

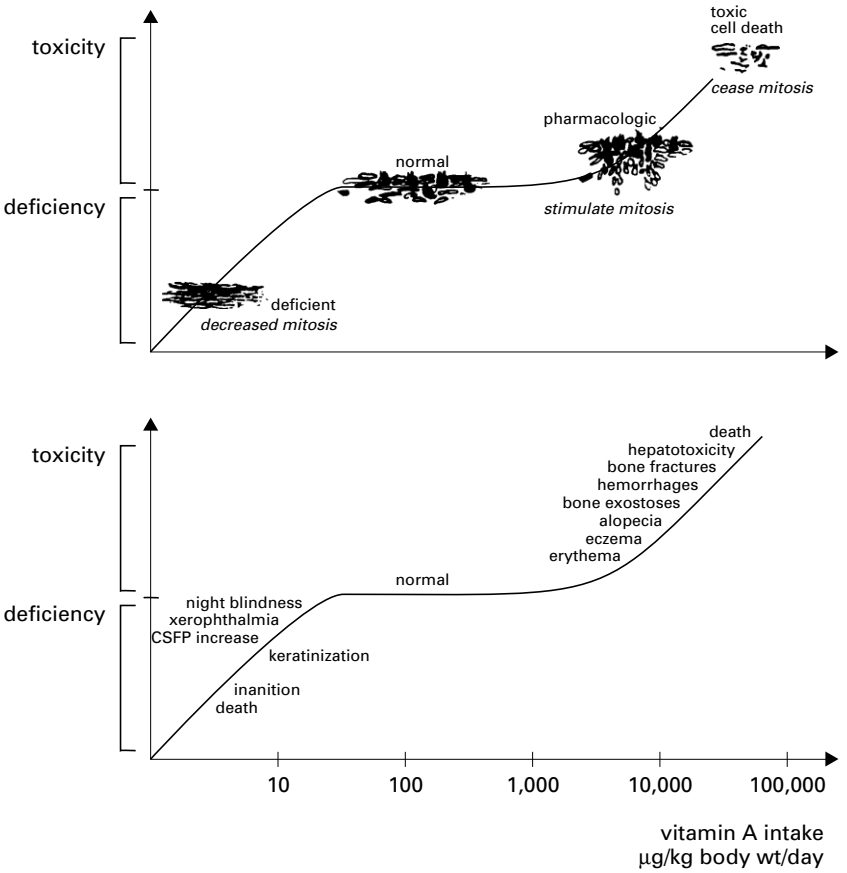

Figure 12.5 Response of a typical mucous epithelium to vitamin A intake (scheme at the top), and clinical symptoms of altered cell function as a result of vitamin deficiency as well as of vitamin A toxicity (bottom curve). Source: Int. Vit. A Consultative Group, Nutrition Foundation, 1980.

in very high doses, vitamin A causes, either acutely or chronically, a large number of adverse effects, including headache, vomiting, diplopia, alopecia, dryness of the mucous membranes, desquamation, bone abnormalities, and liver damage (see Figure 12.5).

Any toxic effects usually result from continuous high daily intake. High intakes of 15 times the RDA can be reached by consuming large amounts of liver or fish liver oils, and food with vitamin A supplements. A high incidence (>20%) of spontaneous abortions and birth defects, including malformations of the cranium, face, heart, thymus, and central nervous system, has been observed in fetuses of women who ingested therapeutic doses of 500 to 1500 µg/kg body weight of 13-cis retinoic acid during the first 3 month of pregnancy. High daily doses of retinyl esters or retinol may cause similar abnormalities.

The mechanisms underlying vitamin A toxicity are very complex, as a sequence of events is triggered. The main toxic effects are related to its function in differentiation and proliferation of cells. The kinetic behavior of vitamin A is largely determined by binding to blood proteins and receptor proteins, and by cellular transport. High intake of vitamin A (hypervitaminosis A) may result in saturation of protein binding which may lead to membrane damage (by free vitamin A).

Vitamin D is necessary for normal bone growth and mineral homeostasis. Exposure of the skin to ultraviolet light catalyzes the synthesis of vitamin D_3 (cholecalciferol) from

7-dehydrocholesterol. Another major form, vitamin D_2 (ergocalciferol), is formed from ergosterol in plants on exposure to ultraviolet light.

Fortified foods (e.g., margarine), milk, eggs and butter are the major sources of vitamin D. The daily vitamin D intake is estimated at 2 μg of cholecalciferol for adults. Presumably, vitamin D pools in the body are replenished in most people by regular exposure to sunlight. The RDA for vitamin D is 5 μg of vitamin D_3 for adults and 10 μg for young adults. Vitamin D is potentially toxic, especially for young children. The effects of excessive vitamin D intake include hypercalcemia and hypercalciuria, leading to deposition of calcium in soft tissues, and irreversible renal damage (nephrocalcinosis) and cardiovascular damage. Although the toxic dose has not been established for all ages, hypervitaminosis D in young children has been related to the consumption of as little as 45 μg vitamin D_3 per day.

Vitamin E is the collective name for an important group of natural products: the tocopherols. There are four members: α, β, γ, and δ, differing from each other in the number and position of the methyl groups attached to the chroman ring, or the saturated carbon side chain. The major and most potent form of vitamin E is α-tocopherol.

The tocopherol content of food (vegetable oils, wheat germ, nuts, green leafy vegetables) varies greatly. During storage and processing large amounts may be lost. The intake of vitamin E is estimated at about 10 mg per day, which is also the RDA. Compared to the other lipophilic vitamins, vitamin E is relatively nontoxic when taken orally. High intake may result in symptoms associated with the pro-oxidant action of vitamin E. Most adults appear to tolerate oral doses of 100 to 800 mg per day.

Vitamin K is necessary for the maintenance of normal blood coagulation. The vitamin is found in green leafy vegetables. Even if large amounts of vitamin K were ingested over a long period of time, no toxic effects were reported. However, administration of a substance structurally related to vitamin K, menadione, may result in hemolytic anemia, hyperbilirubinemia, and kernicterus in the newborn. The underlying mechanism is believed to involve interaction with sulfhydryl groups.

12.3.1.2 Hydrophilic vitamins

To this group belong vitamin C, biotin, niacin, pantothenic acid, folate and the vitamins B: thiamin (B_1), riboflavin (B_2), vitamin B_6 and vitamin B_{12}. Relatively large amounts of these vitamins can be ingested without adverse consequences. They are rapidly excreted from the body, as they are water soluble.

Daily intakes of the antioxidant *vitamin C* (L-ascorbic acid) up to 1 g did not lead to toxic effects. The harmless use of vitamin C is also shown by Figure 12.2. There is a relatively wide margin between the RDA and the toxic dose. If high doses were taken over a long period of time, however, vitamin C appeared to induce toxic effects. Well-known adverse effects after doses as high as 1 g or more are gastrointestinal disturbances such as diarrhea, nausea, and abdominal cramps. Increased peristalsis, resulting from a direct osmotic effect on the intestine, is believed to be the cause. Occasionally, these effects are attributed to sensitization associated with urticaria, edema, and skin rashes. Toxic effects following high doses of vitamin C usually disappear within one or two weeks. They can be prevented by using buffered solutions of vitamin C or by intake after meals.

Thiamin, as thiamin pyrophosphate, is a co-enzyme required for oxidative decarboxylation of α-keto acids and for transketolase in the pentose phosphate pathway. It occurs in considerable amounts in germs of grains, peas, and nuts, and in yeast. Even at very high doses, oral intake of thiamin does not lead to toxic effects; it is rapidly excreted into the urine. Following parenteral or intravenous administration of thiamin, a variety of toxic effects have been reported, but usually only at doses several hundred times higher than the RDA.

Niacin, another hydrophilic vitamin is nicotinic acid. A derivative of this acid, nicotinamide, functions in the body as a component of two cofactors: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Niacin is found in the liver, kidneys, meat and fish, and wheat bran, in the germs of grains, and in yeast. High doses of nicotinic acid, but not of nicotinamide, may lead to vascular dilatation, or flushing.

Vitamin B_6 occurs in two forms: pyridoxal phosphate and pyridoxine (or pyridoxol). Pyridoxal phosphate is the metabolically active form of the vitamin. It serves primarily as a cofactor in transamination reactions. Vitamin B_6 is found in kidneys, liver and eggs. The acute toxicity of vitamin B_6 is low. Toxic effects have not been observed in man following an intravenous dose of 200 mg or oral doses of more than 200 or 300 mg. If taken in gram quantities for months or years, however, vitamin B_6 can cause ataxia and severe sensory neuropathy.

12.3.2 Minerals

A fifth group of substances of vital importance to the body is of mineral origin. Mineral salts comprise a large number of elements necessary for growth and maintenance of the cellular and metabolic systems. In food, either of plant or of animal origin, minerals are present as complex salts. An important factor in the toxicity of minerals is their solubility in an aqueous environment, e.g., the contents of the digestive tract. Sodium and potassium salts are readily soluble in water and thus available for uptake from the intestine. Several other elements, such as iron, calcium, and phosphorus, are present in complex salts which are relatively insoluble. These elements are not easily absorbed from the gut. After intake, the major part of the insoluble salts appears in the feces. In the next paragraphs, dietary intake, RDAs (see also Figure 12.2) and toxic effects are described for several minerals.

Iron is an essential element involved in the transport of oxygen in the body. The iron is bound to porphyrin in hemoglobin (red blood cells) and in myoglobin (muscle cells). Iron is a well-known component of raw liver, beef, millet, and wheat. In vegetables and cereals, it is present as phytate or phosphate. From these relatively insoluble salts, iron is almost unavailable for uptake in the intestinal epithelial cell. Intestinal absorption is possible after the iron has been released, and reduced to the ferrous form.

Poisoning by iron has been reported after the intake of ferrous sulfate. It usually occurs incidentally, and then particularly in children. Acute symptoms are nausea and vomiting within 1 hour, followed by diarrhea and gastrointestinal bleeding and, ultimately, circulatory collapse and death.

The body of an adult contains approximately 1200 g of *calcium*, which is mainly present in the bones (body-oriented). Calcium is present in dairy products, including milk and cheese. The daily intake of calcium varies greatly with age and sex, ranging from 530 to 1200 mg. Intestinal absorption of calcium is variably influenced by a large number of factors, such as vitamin D, protein, lactose, phytic acid and dietary fiber, fat, and phosphate. From relatively high intakes, above 800 mg/day by normal adults, approximately 15% was absorbed. The RDA for calcium is 800 mg for adults and 1200 mg for young adults. In general, calcium toxicity is rarely observed. No adverse effects have been observed in many healthy adults consuming up to 2500 mg of calcium per day. However, high intakes may interfere with the intestinal absorption of essential elements such as iron and zinc. Ingestion of very large amounts may result in hypercalcemia, and decreased renal function in both sexes.

Sodium is the major cation in blood and extracellular fluids. The physiological function of sodium is primarily the regulation of osmolarity and membrane potentials of cells. The

estimated need for sodium depends on the degree of physical activity and ambient temperature, and ranges from 300 to 500 mg/day for healthy adults.

In the majority of foodstuffs, the sodium originates from the addition of sodium chloride. Single excessive intake of sodium chloride leads to water transfer from the cells to the extracellular space, ultimately resulting in edema and hypertension. As long as the water need can be met, the kidney can excrete the excess of sodium and this effect is reversible. Continuous overconsumption of sodium (2500 mg/day), particularly in the form of sodium chloride, has been found to cause hypertension. Based on these data obtained in human studies, it is obvious that the safety margin for sodium is relatively small.

Potassium is the major intracellular cation. Its concentration in the cell is 30 times higher than in blood and the interstitial fluid. The low extracellular potassium concentration is of high physiological importance in the transmission of nerve impulses (in order to control the skeletal muscle contractility) and the maintenance of normal blood pressure. Dietary sources of potassium are potatoes, soya flour, and fresh fruits. The estimated daily need for potassium is 2000 mg. The safety margin for potassium is relatively small: an RDA of 2000 mg and a toxic dose of 18,000 mg/day.

Acute intoxication of adults has been reported to result from sudden enteral or parenteral potassium intakes up to about 18 g (hyperkalemia). Acute hyperkalemia may lead to cardiac arrest. High potassium blood concentrations may also result from renal failure, adrenalin insufficiency and shock after injury.

Chloride, the major inorganic anion in the extracellular fluid, is necessary for fluid and electrolyte balances. Further, it is an essential component of gastric juice. The only known "dietary" cause of hyperchloremia is dehydration.

Magnesium is primarily present in muscles, soft tissues, extracellular fluid, and bones. About 70% of the daily magnesium intake is covered by the consumption of vegetables and grains. There is little or no evidence that large oral intakes of magnesium are harmful to people with normal renal function. Impaired renal function is often associated with hypermagnesemia resulting from magnesium retention. Early symptoms include nausea, vomiting and hypertension. Hypermagnesemia occurs most frequently following the therapeutic use of magnesium-containing drugs, and not on dietary ingestion of magnesium.

Phosphorus is an essential mineral component of bone tissue, where it occurs in the mass ratio of 1 phosphorus to 2 calcium. Phosphorus is present in nearly all foods. The mean daily intake is estimated at about 1500 mg, while the RDA is 1200 mg. In a number of species, excess phosphorus, i.e., a calcium–phosphorus ratio of 0.5, led to a decrease in the calcium blood level and secondary hyperparathyroidism with loss of bone. The phosphorus levels in normal diets are not likely to be harmful.

12.3.3 Trace elements

Examples of the large group of trace elements are: zinc, iodine, selenium, copper, manganese, fluorine, chromium, and molybdenum. Trace elements are often co-factors of enzymes, and are therefore essential nutrients. The range between the dose necessary for good health and the toxic dose is relatively small for a number of trace elements (see Table 12.5.1). The trace elements that will be discussed here have an intermediate safety margin (10-33): zinc, copper, selenium, and fluorine.

Zinc is a co-factor of a variety of enzymes mediating metabolic pathways, such as alcohol dehydrogenation, lactic dehydrogenation, superoxide dismutation, and alkaline phosphorylation. It occurs especially in meat, (whole) grains and legumes. The RDA for zinc is 12 to 15 mg, depending on the age, while the zinc intake is about 10 mg/day.

Acute toxicity, including gastro-intestinal irritation and vomiting, has been observed following the ingestion of 2 g or more of zinc in the form of sulfate. Effects of relatively low intakes are of greater concern. After dietary intakes of 18.5 or 25 mg by volunteers, impairment of the copper state has been observed. Further, daily intake of 80 to 150 mg during several weeks caused a decrease in the high-density lipoprotein serum level.

Zinc intakes of 20 times the RDA for 6 weeks led to impairment of the immune system, and intakes of 10 to 30 times the RDA for several months led to hypercupremia, microcytosis, and neutropenia. For these reasons, chronic ingestion of zinc exceeding 15 mg/day is not recommended.

Copper is also incorporated in a number of enzymes including cytochrome oxidase and dopamine hydroxylase. It is found in green vegetables, fish, and liver. The copper intake varies from 1.5 to 3.0 mg/day for adults. This is also the RDA.

In general, toxicity from dietary sources is extremely rare. Liver cirrhosis and disturbances of brain functions (e.g., coarse tremor and personality change) have been reported. No adverse effects are to be expected from intakes of up to 35 mg/day for adults. Storing or processing acidic foods or beverages in copper vessels can add to the daily intake and cause toxicity from time to time.

Selenium can be of plant as well as of animal origin. It occurs in seafoods, kidneys, liver, and various types of seeds, e.g., grains. The level in plants depends on the selenium content of the soil in which the plants are growing. Selenium plays an important role in (lipid) peroxide detoxication. The detoxication is catalyzed by a selenium-containing enzyme, glutathione peroxidase.

The daily intake of selenium varies from 80 to 130 μg. The RDA is set at 150 μg. The toxic dose is about 30 times the RDA. Acute intoxication has been reported after ingestion of about 30 mg. Symptoms were nausea, abdominal pain, diarrhea, nail and hair changes, peripheral neuropathy, fatigue, and irritability. Chronic dietary intake of approximately 5 mg/day has been found to result in fingernail changes and hair loss (selenosis). In the seleniferous zone of China, a daily dietary intake of 1 mg of sodium selenite for more than 2 years resulted in thickened but fragile nails and garlic-like odor of dermal excretions.

Fluoride is present in low but varying concentrations in drinking water (1 mg/l), plants (e.g., tea), and animals (fish, 50 to 100 mg per 100 g). It accumulates in human bone tissue and dental enamel. Its beneficial effects on dental health have clearly been demonstrated.

Fluoride is toxic, if consumed in excessive amounts. The normal daily intake is 1 to 2 mg. Daily ingestion of 20 to 80 mg of fluoride leads to fluorosis. This is characterized by calcification resulting in effects on kidney function, and possibly muscle and nerve function. A single intake of 5 to 10 g of sodium fluoride by a 70 kg adult has been reported to cause death. Fluoride intakes above the level of 10 mg per day are not recommended for adults.

12.4 Summary

Two points are of high toxicological importance with respect to nutrient intake: the margin between physiological need and toxic intake and the possible interaction between food components. The nutrients are commonly divided into two groups: the macronutrients (fats, carbohydrates, proteins) and the micronutrients (vitamins and minerals, including trace elements). For the intake of nutrients, recommended dietary allowances (RDAs) are set. These are defined as the intake levels that meet the needs of practically all healthy persons. RDAs are considered to be safe.

As far as the intake of macronutrients is concerned, it is important to know from a toxicological point of view that the dietary levels of the three categories of macronutrients

are closely related to each other; they are all sources of energy. An increase in dietary intake of one category will result in decreases in intake of the others.

A variety of toxic effects may result from fat intake. The higher incidence of cancer is well-known. The role of fat in carcinogenesis may be ascribed to tumor promotion. Further, effects that result from lipid peroxidation may be induced. Not only membranes and enzymes have been shown to be primary targets of peroxidation products, but also DNA. Indirect effects may also be associated with dietary fat intake. The increase of tumor incidence in rats treated with aflatoxin B1 and diethylnitrosamine following high-fat intake is believed to be caused by activation of cytochrome P-450 enzymes. Interactions between fat and other food components have also been reported at the level of detoxication. High intake of polyunsaturated fatty acids may lead to depletion of the antioxidant vitamin E.

Adverse effects after high carbohydrate intake are attributed to a decreased intake of the other macronutrients, rather than to actual toxicity of the carbohydrates. Special attention should be paid to the high-risk groups that are congenitally intolerant to particular food components, e.g., lactose.

Protein intakes slightly higher than the physiological needs are generally believed to be safe. High protein intake has been reported to result in acceleration of the processes that lead to renal (glomerular) sclerosis. Oxidation of sulfur-containing amino acids has been shown to form toxic products. Protein intake may also indirectly lead to the induction of toxic effects. Secondary amines from fish protein may react with nitrites originating from vegetable intake, and this may lead to the formation of nitrosamines. Dimethylnitrosamine has been shown to induce tumors in experimental animals.

An important determining factor in the induction of toxic effects by micronutrients is their solubility. Intake of lipophilic vitamins such as vitamins A and D poses the highest toxicological risk, as they can accumulate in the body. Relatively large amounts of the hydrophilic vitamins can be ingested without adverse consequences. They are rapidly eliminated, as they dissolve well in water. Minerals occur in food as complex salts. Several elements are not easily absorbed from the gut, as they occur as relatively insoluble salts.

If consumed at very high doses, the lipophilic vitamin A causes a large number of toxic effects, either acutely or on the long term, including liver damage and developmental disturbances. The main toxic effects are related to its function in differentiation and proliferation of cells. The kinetic behavior of vitamin A is largely determined by its binding to blood proteins and receptor proteins. Well-known effects after excessive intake of another lipophilic vitamin, vitamin D, are hypercalcemia and hypercalciuria, leading to deposition of calcium in soft tissues, and irreversible renal and cardiovascular damage.

A third lipophilic vitamin, the antioxidant vitamin E, is relatively non-toxic when taken orally. High intake may result in symptoms associated with the prooxidant action of the vitamin.

As far as the toxic effects of the hydrophilic vitamins are concerned, the gastrointestinal disturbances after high intake of vitamin C are well known. The toxic effects of vitamin C usually disappear within 1 or 2 weeks.

In general, the availability of the mineral elements iron, calcium, and phosphorus after oral intake is too low to induce toxic effects. These elements are present as relatively insoluble salts, and thus almost unavailable for absorption from the intestinal content.

Intake of the trace element selenium is known to lead to the induction of toxic effects by the element itself as well as adverse effects on the detoxication of other substances. Acute poisoning symptoms following high doses has been reported to include nausea, and nail and hair changes. In areas where the selenium content of the soil is low, disturbances of the detoxication of substances that cause lipid peroxidation may be expected. The detoxication is catalyzed by the selenium-containing enzyme glutathione peroxidase.

Reference and reading list

This chapter is largely based on:

Basu, T.K., (Ed.), *Drug–Nutrient Interactions.* Worcester, Billings & Sons, Ltd., 1988.

Comporti, M., Lipid peroxidation. Biopathological significance. Mol. Aspects *Med.* 14, 199–207, 1993.

Davidson, S., R. Passmore, J.F. Brock and A.S. Truswell, (Eds.), *Human Nutrition and Dietetics,* 7th edition. Edinburgh, Churchill Livingstone, 1979.

Guengerich, F.P., Influence of nutrients and other dietary materials on cytochrome P-450 enzymes. *Am. J. Clin. Nutr.* 61 (3 Suppl.), S 651-S 658, 1995.

Hathcock, J.N., (Ed.), *Nutritional Toxicology,* Volumes I, II and III. New York, Academic Press, Inc., 1982, 1987 and 1989, respectively.

Recommended Dietary Allowances (RDAs), Subcommittee on the 10th edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. Washington, D.C., National Academy Press, 1989.