Biological Responses of Elements

9

Monica Nordberg and M. George Cherian

Contents

9.1 An Introduction to Biological Responses of Certain Elements

Medical geology is defined as the science dealing with the relationship between natural geological factors and health problems in man and animals. The geographical distribution of trace elements and metals in nature can explain "natural deficiency or toxicity," which includes the occurrence of health problems, diseases, and adverse health effects endemically seen. It is a broad subject and it attracts interdisciplinary collaboration and contributions. A relationship between humans and the ecosystem, environment and life, and environment and illness exists, and geological factors are of major interest in the environment in this respect (see also Chaps. 8 and 24, this volume).

Biological effects in response to environmental exposure of elements constitute two parts, deficiency and toxicity, which are the themes of this chapter. Under normal conditions human nutritional deficiencies may occur due to environmental, sociological, and genetic influences. Thus deficiency syndromes are an expression of multiple simultaneous effects. Functional abnormalities related to specific nutrients may be identified by the biological role of the nutrient, in controlled physiological experiments and by multivariate analysis of outcomes. Model systems and dose response experiments allow measurements of deficiency effects at different levels of physiological states and at different stages in the life cycle. Such experiments provide a basis for understanding the roles of nutrients in human physiology and the biological consequence of deficiencies. Nutritional deficiencies of certain minerals in soil have resulted in diseases in populations. For example, zinc deficiency in Iran and selenium deficiency (Keshan disease) in China were due to mineral deficiencies in soil. In most western countries, farmers are aware of this problem, and they test the soil every year and add the deficient nutrients before planting their crops. Thus they get better crops and also take care of the nutritional status of the population.

M. Nordberg (✉)
Institute Environmental Medicine Karolinska Institutet, Stockholm, Sweden
e-mail: Monica.Nordberg@ki.se

M.G. Cherian
Department of Pathology, University of Western Ontario, London, ON, Canada

O. Selinus et al. (eds.), *Essentials of Medical Geology: Revised Edition*,
DOI 10.1007/978-94-007-4375-5_9,

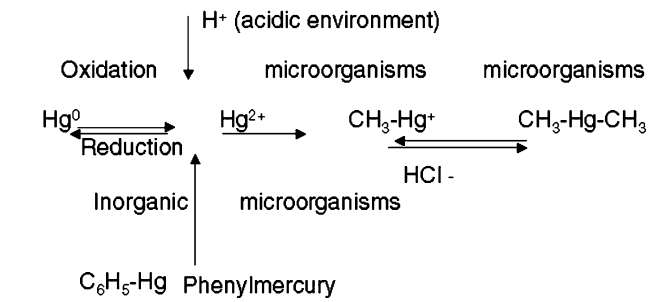

Fig. 9.1 The cycle of mercury

Primary nutritional deficiencies are caused by adverse economic conditions, customs, and food choices that limit dietary variety and thus nutrient availability. Conditioned (secondary) deficiencies are caused by non-dietary factors, especially illnesses and iatrogenic conditions that interfere with absorption, utilization, or retention of nutrients. In many instances, especially among the poor, combined effects of low intakes and conditioning factors result in deficiency disease. The conditioning factors can also give rise to toxicity.

Toxicity can occur either due to high bioavailability of elements or due to interactions of trace elements in the environment. To follow changes in the eco- and biological systems and their relationship to exposure conditions, different forms of monitoring, e.g., environmental and biological, are performed as illustrated in Table 9.1. These may involve mode of exposure, dose, and effects (see also Chap. 26, this volume).

Essentiality and toxicity of trace elements need to be in balance. Otherwise, adverse health effects to the organism will develop with cellular functional changes as the first sign of toxicity, followed by organ damage, and subsequent manifestation of illness as the end point. Most studies on toxicity of metals have been performed with the assumption that intake of essential trace elements are on a "normal basal" level. When the dietary level of essential trace elements is low, toxicity can occur at much lower concentration levels of the non-essential elements than previously regarded as toxic dose levels for these elements. The recommendation for supplementation of daily intake of essential metals in certain cases can exceed the dose that may cause toxicity. With that background a more intense collaboration between researchers in toxicology and nutrition was initiated on an international level (WHO 2002).

Toxicity of metals depends on bioavailability, species, and exposure conditions. Metals that are essential for life can also cause adverse health effects if exposure is excessive or if the chemical species or exposure route is different from the physiological route. Low iron status, and other nutritional factors such as low intake of protein, calcium, and zinc, can increase the toxicity of toxic metals such as cadmium and lead. Although an element is classified as essential to the organism it can cause toxicity with excessive exposures and interactions. The environmental level of metals in the ecosystem is influenced by industrial emissions and other human activities. Recycling of batteries and modern electronic equipment materials increases concentrations of metals such as cadmium, mercury, and semi- and superconductor materials like gallium and indium in the ecosystem. The interactions between ecosystem and these human activities may result in excessive exposure to metals (see also Chap. 4, this volume).

The acidification of lakes and soils due to emissions of sulfur and nitrogen oxides results in changes in the mobility and promotes chemical conversion of metals and may result in chemical species of certain metals with greater toxicity than the parent compound. Aluminum, arsenic, cadmium, and mercury constitute examples of elements with increased mobility whereas selenium has decreased mobility in an acidified ecosystem. With increased acidification of lakes, increased mercury concentration in the fish has been reported due to increased bioavailability of methylmercury. It is reported that the concentration of metals in fish and crops can vary with change of pH in lakes, sediments, and soils.

Environmental biochemistry of metals provides special emphasis on chemical reactions that transform metals in the environment into species or compounds of the element that are either more toxic or less toxic. For example, chemical reactions like methylation and demethylation can alter the toxicity of mercury and arsenic. It is known that both bacteria and vitamin B_{12} can methylate mercury in sediments.

Medical geology is of global concern not only for humans but also for plants and animals. Tissue samples from penguins and seals from the Antarctic that were analyzed for cadmium and copper showed increased concentrations in samples from areas that were regarded as non-polluted. This might be explained by the geology of the Antarctic. Oysters from New Zealand can be high in cadmium but binding to various bioligands can vary their intestinal absorption pattern, and thus affect toxicity.

The adverse health effects of mercury depend on the species of mercury. Figure 9.1 shows the cycle of mercury in the ecosystem. Inorganic mercury, mercury vapor, methylmercury, and various other mercury compounds exist in the ecosystem due to bioconversion, and can be transformed to a stable form of methylmercury by bacteria and vitamin B_{12}. This is the most toxic form of mercury for humans because it is easily absorbed (about 99%) from the gastrointestinal tract and retained in the body with high distribution to the brain.

Table 9.1 Different forms of monitoring of metals and their relationship to exposure, dose and effects

Emission	Exposure	Internal dose indicators	Biological effects
Sources/rates/patterns	Air	Absorbed dose	Bioindicators of effects
	Water	Body burden	Early health effects
	Soil	Target tissue concentration	Overt health impairment
Source characterization and emissions monitoring	Environmental monitoring	Biological monitoring	Health monitoring

From Clarkson et al. (1988)

Table 9.2 Factors influencing uptake of trace elements and metals

Concentration of agent
Chemical and physiological properties of the agent and the soil
Particle size
Physiological factors: age and nutritional status
Any existing disease
Genetic make up

The aim of this chapter is to illustrate the relationship between deficiency and toxicity of trace elements and to give examples of diseases related to geology-medical geology or medical geology. Special attention is paid to iodine, iron, selenium, cadmium, and mercury and this chapter also includes a few other trace elements. These elements are selected for discussion because of their known role in certain diseases or their interactions that can lead to diseases (see also Chaps. 5, 6, 22, and 25, this volume).

9.2 Metals and Geo-Environment

Human exposure to metals generally occurs through food, drinking water, and air. The drainage of contaminants from farmland is a major source of toxic metals in well water in rural areas. In several cities in developing countries, air pollution with metals has become a major problem. Occupational exposure mostly takes place via inhalation of metal fumes and dust where the trace elements exist as oxides, sulfides, or in the elemental form. Exposure to metals can be monitored in various ways: the exposure sources, the type of indicators, and the biological effects in general can be all documented in such monitoring methods (Table 9.1).

9.2.1 Toxicity

Paracelsus (1493–1541) stated that everything is toxic, it is just a matter of dose. Trace elements are important for life. Both deficiency and toxicity can cause adverse health effects. Many metals constitute part of the structure or cofactor of the enzymes and play important roles for the biological activity of enzymes and vitamins. Zinc plays an essential role in zinc-dependent enzymes such as alcohol dehydrogenase and cobalt in vitamin B_{12}.

Upon exposure to high concentrations of non-essential elements clinical disease or death can occur in exposed individuals, and in most acute toxic cases, the effect is directly related to the dose. At a lower dose range, less severe effects might occur after a long latent period. In most cases, the higher the dose, the shorter the latency period for appearance of toxic effects.

Risk assessment in environmental medicine serves as a basis of preventive action in order to avoid adverse health effects in general populations exposed to chemicals. To discuss toxicity, it is important to define concepts such as factors influencing uptake (Table 9.2), critical organ, critical dose, critical effects, and biological half-time. The organ or tissue where the exposed chemical can give rise to a critical effect is known as the critical organ. Normally, the critical organ is the organ where the earliest adverse effect occurs in an individual. Critical concentration is the concentration of the chemical, which can cause the earliest adverse effect in the critical organ in an individual or population (Nordberg and Nordberg 2002) (see also Chaps. 22 and 26, this volume).

In order to prevent toxicity and maintain quality of life, it is important to find various sensitive chemical or biological indicators for early detection of effects of metals in the critical organ. Each metal and sometimes each species of metal is unique with regard to its critical organ and toxicity. A typical example for this is the different forms of mercury and their different target organs for toxicity. Mercury vapor and methylmercury exposures can affect the brain while inorganic forms of mercury can affect the kidney. The cornerstone to develop a metabolic model constitutes knowledge of absorption, distribution, excretion, biotransformation, and biological half-time for specific species of the metal.

In order to understand the toxicity of metals and the role of geology (Tables 9.3 and 9.4), it is important to have information on concentration levels of metals in water, air, and soils in a particular geographical area (see also Part II, this volume).

Geological factors such as availability of trace elements and metals can be reflected in the occurrence of diseases in man and animals. If plants actively take up a metal, it can

Table 9.3 Health risk evaluation of agents in soil

Agents
Concentration and quantities
Exposure situation
Type of soil/rock
Mining and volcanic activity
Bioavailability
Health effects

Table 9.5 Human metal/metalloid carcinogens

As and inorganic compounds	1980
Chromium (VI)	1990
Nickel and compounds	1990
Cadmium and compounds,	1993
Beryllium and compounds	1993

Table 9.4 Examples of relationship between elements, geology and health effects as expression of medical geology

Metal	Activity	Disease
Arsenic and drinking water	Well-drilling in Bangladesh and cattles in US	Cancer
		Keracytoses
Cadmium	Japan	Itai-Itai
Cesium as 137	Radioactive release chernobyl	Cancer
Copper	Genetic defects	Menke's disease placenta
		Wilson disease liver
		Indian liver cirrhosis liver
	Copper in kitchen utensils	
Selenium	Farming in China	Kashin-Beck; Keshan
	Farming in Finland	cancer & heart disease

result in high exposures to people living in that area. The increased amount of cadmium in rice was the cause of "itai itai" disease in Japan, and also in Shipham in the UK. Nutritional deficiencies (iron, calcium, and vitamin D) also might have played a role in itai itai disease.

9.2.2 Neurotoxicity

Certain forms of metals such as methylmercury can cause neurotoxicity. Certain forms of mercury such as mercury vapor and methylmercury can easily cross the blood–brain barrier. Mercury can bind with critical ligands and cause a direct toxic effect in the cell. However, for cadmium neurotoxicity, the uptake in brain and the mechanism behind neurotoxicity are more obscure. Lactating pups of dams exposed to cadmium showed changes in the serotonin levels. Because cadmium does not pass the blood–brain barrier, this observation remains controversial. Other factors like interference of cadmium with zinc or calcium metabolism and the presence of a specific form of metallothionein (MT-3) in the brain should also be considered in the neurotoxicity of metals. Lead is known to cause central nervous system (CNS) toxic effects in children, but it may cause damage to peripheral nerves in adults because of the differences in permeability to the blood–brain barrier.

9.2.3 Carcinogenicity

A few metals or metalloids (arsenic) have been classified by the International Agency for Research on Cancer/World Health Organization, (IARC/WHO) (IARC 1980, 1990, 1994) to be carcinogenic in humans, i.e., group 1 as presented in Table 9.5. These classifications are based on epidemiological studies and detection of tumors in certain organs depending on the mode of exposures. A number of metals have been shown to be carcinogenic in animals, especially after injection of metal salts, but only a few have been classified as human carcinogens, i.e., group 1.

9.3 Protective Mechanisms

There are several binding sites for metals in the cells, and therefore, a number of mechanisms may be involved in the cell to protect it from developing toxic effects, as shown in Table 9.6.

9.3.1 Importance of Various Proteins

New families of proteins, important for protecting the cell from toxic insults by reactive oxygen species (ROS) and also

Table 9.6 Examples of protective mechanisms in metal toxicology

Metal binding proteins
Localization in the cell
Metallothionein in cytoplasm/nucleus
Lead-binding inclusion bodies in kidney
Detoxification by binding to glutathione or amino acids
Change of pH in lysosomes
Interaction between metals e.g. selenium-mercury, cadmium-zinc
Protein intake
Iron status
Genetic polymorphism
Methylation
Demethylation

heat shock proteins, have been identified after exposure to metals. Although these proteins are found in low basal levels in cells, they are inducible at a transcriptional level when exposed to metals (Piscator 1964). The genes coding for metallothioneins (MTs) and heat shock proteins are present in most of the organisms, and their induction after exposure to metals plays an important role in protection against metal toxicity. There are several review articles published on metals and stress proteins (Goyer and Cherian 1978; Goering and Fisher 1995; DelRazo et al. 2001), and they describe the specificity of certain metals to induce various heat shock proteins, and some of the similarities on gene expression for these proteins and MTs. The metal regulatory elements (MRE) present in the metallothionein gene and metal transcription factor (MTF-1) are important factors that may control the mechanisms of induction of these proteins after exposure to certain metals (Seguin 1991; Radtke et al. 1993). Both essential (zinc and copper) and non-essential (cadmium and mercury) metals can induce the synthesis of MTs and also bind to them. Thus, these proteins may have a role in the metabolism of essential metals and protection against the toxicity of metals (Cherian and Nordberg 1983; Cherian 1995, 1997).

9.3.2 Metallothionein

The structure, chemicophysical properties, and the physiological/biological functions of MTs in several organisms have been investigated for the last 55years. Metallothionein is a family of proteins with low molecular weight (6,500Da) with a unique capacity to bind seven metal ions through the 20 cysteinyl groups. Of the 61 amino acids of this protein, 20 of them are cysteines. In MT, divalent zinc and cadmium are bound tetrahedrally, with both primary and bridging sulfur bonds. It may bind with 12 monovalent copper trigonally. Two distinct metal binding domains, the α- and β-clusters have been characterized in MT by both NMR solution structure and crystallization. The purified MTs generally contain 5–10% metals as zinc, cadmium, mercury, or copper. The characteristic properties of MT (Kägi and Nordberg 1979) are listed in Table 9.7.

The definition of the MT super family follows the criteria set for polypeptides that have common features with equine renal MT. The four major forms of groups of MT consist of MT-1, -2, -3, and -4 isoforms. Mammalian MT-1 and -2 forms are present and expressed in almost all tissues. However, the number of isoforms differs, as MT-1 exists in many subisoforms, whereas only one isoform for MT-2 has been identified. MT-3 has seven additional amino acids and contains a total of 68 amino acids with differences in charge characteristics when compared to isoforms MT-1 and -2. The MT-3 isoform was identified years after characterization of MT-1 and -2 as a growth inhibitory factor (GIF) in the brain. At the N terminal region of MT-3 an additional threonine is inserted and 6 additional amino acids consisting of glutamic acid and alanine are present as a loop at the C terminal region. Thus MT-3 differs from MT-1 and -2 in its amino acid sequence. Another difference in the sequences of the MT-3 form is the presence of a proline close to the N-terminal region, which contributes to the growth inhibitory effects of MT-3. The threonine in MT-3 increases the acidity and the charge surface facilitates the interaction of MT-3 with other biological constituents. MT-4 consists of 62 amino acids with one glutamate inserted and is specific for squamous epithelium and expressed in keratinocytes. There are 14 human MT genes that are localized on chromosome 16q13–22. Of these six are functional, two are not, and six have not been characterized.

MT is often related to toxicokinetics and biochemistry of essential and non-essential metals such as zinc, cadmium, mercury, and copper. *In vivo* binding to other metals/metalloids such as selenium and bismuth is not yet understood. Although it is mainly an intracellular protein, MT has been detected in small amounts in blood and urine.

Several functions have been proposed for MT, and they are listed in Table 9.8. They may play an important role in the homeostasis of essential metals such as zinc and copper. It has been demonstrated that mammalian fetal liver contains very high levels of MT bound to these metals, and it may act as a metal storage protein during gestation similarly to ferritin as an iron storage protein. In fetal and newborn liver, MT is localized in the cell nucleus and cytoplasm, but during growth, MT is degraded and the levels of zinc and copper are maintained at a low basal level. In adults, the low levels of MT in the hepatocytes are detected in areas around the wound after partial hepatectomy and surgery. Thus, MT may serve as a storage protein for zinc during development and other conditions when the requirement for zinc is high. In addition, because of its high affinity for

Table 9.7 Characteristics of metallothionein

1. Molecular weight 6,000–7,000, 61 amino acids (aa)
2. 20 cysteine (30%), N-acetylmethionine, C-alanine, no aromatics, no histidine
3. Metal content (cadmium, zinc, copper, mercury) 5–10% w.w.
4. Absorption 250nm (cadmium), 225nm (zinc), 275nm (copper), 300nm (mercury)
5. Induced synthesis by cadmium, zinc, copper and mercury
6. No disulfide bonds
7. Heat stability
8. Cytoplasmic and nuclear localization
9. Unique amino acid sequence

Table 9.8 Functions of metallothionein

1. Metabolism of essential metals
2. Detoxification of metals
3. Protection from metal toxicity
4. Storage of metals
5. Protection from oxidative stress
6. Cellular proliferation and differentiation

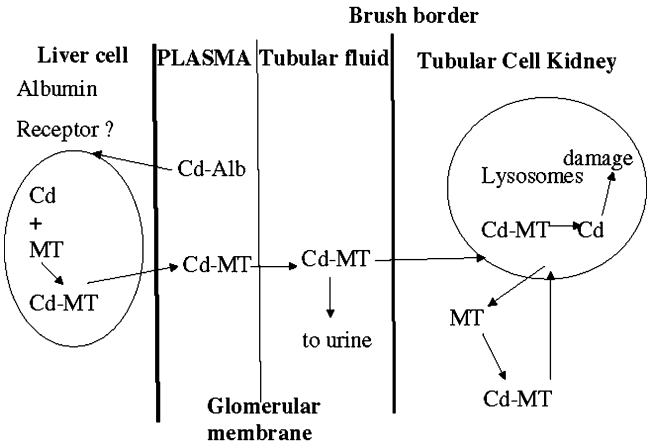

Fig. 9.2 Model of transport of cadmium in blood

metals, MT can detoxify the toxic effects of certain non-essential metals such as cadmium and mercury.

Cellular membranes are targets for metals, and MT may play a role in protection of the cell from metal toxicity. However, the release of Cd-MT from liver and other tissues can cause toxic effects. Membrane damage caused by Cd-MT in the renal tubule is most likely explained by a direct interference of cadmium on calcium transport in renal membranes and might explain chronic toxicity of cadmium on the kidney. Metals like mercury, copper, and cadmium are continuously accumulated in liver and kidneys with a major part bound to MT. Cd-MT is efficiently transported through the glomerular membrane and actively taken up by the renal tubular cells, which causes damage to the cell.

Expression of MT in different tissues is influenced by the exposure to metals and their accumulation. Therefore these proteins could be used as a biomarker of toxic metal contamination at an environmental level and as a biomarker of toxic effects in an individual.

A number of different techniques and methodologies have been used for the quantification of MTs. The detection is based on the redox properties of the thiol groups in the molecule, for electrochemical methods, on saturation with metal ions, for indirect quantification methods, and the immunoreactivity with antibodies for immunochemical methods. These methods are widely used to determine the levels of MT in tissues and biological fluids, depending on their detection limit. Still, certain technical problems exist with the determination of MT in certain biological samples.

When MT is isolated from various tissue samples, the content of metal ions may differ depending on tissue factors and the exposure levels of metals. In most cases, isolated MT is completely saturated with metals. It is well known that atmospheric oxygen can easily oxidize MTs, which results in the formation of disulfide bonds with "free" thiol groups. In isolation methods, a reduction agent, such as 2-mercaptoethanol or dithiothreitol, is used to prevent the disulfide bond (S–S) formation. The immunoassays of MT in biological samples may provide limited values because of the lack of antibodies, which can cross-react with all the forms.

Increased tissue concentration of MT-1 and -2 may indicate increased exposure to certain elements. MT-3 has not been shown to be inducible with metal exposure, but it may play a role in zinc metabolism and other elements in the brain. A mechanistic model for cadmium and MT illustrates the chronic toxic action of cadmium in renal tubular cells and the development of adverse health effects after low-dose chronic exposure.

Because of its low molecular weight and related efficient glomerular filtration in the kidney, the binding of Cd to MT in blood plasma serves as one of the modes (Fig. 9.2) of transport of cadmium from liver and other tissues to the kidney. The binding of cadmium to MT and other low molecular ligands in plasma and tissues may play a role in the tissue distribution of cadmium after uptake from the intestine. The absorption of cadmium in the gastrointestinal tract may involve divalent metal transporters (DMT-1), and it could also be influenced by MT synthesis in the intestine. Because both cadmium and iron are taken up by DMT-1, a direct competition by these metals in the intestinal level cannot be ruled out. Previous studies have shown that the gastrointestinal (GI) absorption of cadmium in humans may depend on the iron status (Flanagan et al. 1978). Uptake and distribution of cadmium occurs mainly in the initial phase in a form where cadmium is bound to albumin in plasma. A report suggests that iron deficiency can increase levels of MT-1 in bone marrow of

rats with hemolytic anemia with unchanged hepatic and reduced renal MT, and it may indicate that MT-1 levels in blood reflect erythropoietic activity (Robertson et al. 1989).

MT levels in the liver and kidneys may serve as potential indicators of environmental exposure to cadmium, zinc, and copper. The extremely long biological half-time of cadmium in the kidney (15–20years in humans) may be due to its binding to intracellular MT. Thus, MT can immobilize cadmium intracellularly, and can play a role in the kinetics of cadmium and protection from metal toxicity (Nordberg 1998; Nordberg and Nordberg 2000).

9.3.3 Metabolism and Kinetics of Trace Elements and Toxic Metals

The metabolism and kinetics of trace elements involve binding to various proteins. The specific role of MT in the binding of cadmium and zinc has been described in the previous sections.

A similar role for MT in the kinetics for copper also has been shown (Bremner 1987). In certain diseases like Wilson's disease, the excretion of copper is impaired and results in accumulation of copper in the liver. Initially, the toxicity of copper may be prevented by induced synthesis of MT, and its binding to copper. At a later stage, the cells are unable to synthesize MT, and binding capacity of MT may get saturated. The excess copper ions or copper-saturated MT may cause toxicity to liver cells.

9.4 Biological Monitoring of Metals and Trace Elements

To study the toxicity of metals in a population and protect public health, biological monitoring of metals has been performed in various populations such as lead in children and pregnant women and mercury in people with dental amalgam.

The use of MT as a potential biochemical indicator for environmental cadmium exposure has been tried by analyses of tissue samples from moose and reindeer from the northern part of Sweden and penguins and seals from the Antarctic. Cadmium was found to be a major metal component in MT even from this area that is regarded as non-polluted. Human tissue samples from autopsy have been used as potential indicators of environmental exposure to cadmium in Canadians. For bioindicators for metals and their potential use in risk assessment see Clarkson et al. (1988).

The quality of the analyses in biological monitoring depends on a number of factors. The time of collection and storage of specimens for analysis of metals or species of metal (inorganic or organic) should be controlled. The difficulty in interpretation of such results and accuracy of the method also should be considered in such studies. Among the sources of error in biological monitoring of environmental exposure are physiological factors such as variations in the biological material, age, diet, smoking, alcohol intake, and concurrent exposure to other compounds and drugs that can affect metabolic changes. Other factors may involve species-dependent kinetics of elements and simultaneous exposure to mixed species of an element.

The external contamination is a major problem in trace element analysis in biological samples during collection, and some of the special techniques can be successfully performed only by trained personnel. The contamination might arise from both the collection procedure and the storage container itself. Good hygiene should be practiced when collecting specimens, i.e., smokers should not collect samples for cadmium analyses. Contamination might also occur in sampling for zinc and aluminum where powder used as lubricant in disposable gloves can contribute to contamination. The material of the containers also can contribute to errors. Specific care has to be taken upon monitoring of aluminum. Quartz knifes are, for example, recommended for the handling of tissue samples in order to avoid contamination with chromium or nickel. Metal analysis is usually performed by atomic absorption spectrometry (flame, graphite furnace, and electrothermal), and also by X-ray fluorescence spectrometry.

9.5 Specific Metals

Several trace elements are found to be essential to human health, and they are iron, zinc, copper, chromium, iodine, cobalt, molybdenum, and selenium (WHO 2002). Other elements that might have a beneficial effect and probably are essential for humans are silicon, manganese, nickel, boron, and vanadium, and they may constitute a second group of trace elements of human concern. If they are accepted as essential trace elements, a biological requirement should be demonstrated at appropriate dose levels (WHO 2002). Some of these elements can be toxic, and those that can interact with others are discussed here.

9.5.1 Aluminum

9.5.1.1 Aluminum—Plasma

Aluminum is found in several human organs, including lungs. Pulmonary fibrosis has been reported after inhalation of aluminum in certain industrial operations and in mining. Aluminum is mainly excreted through urine, and kidney damage can increase its retention.

Aluminum administration to experimental animals can produce osteomalacia and cause neurotoxicity in certain animals with neurofibrillary tangle formation. The role of aluminum in Alzheimer's disease is still controversial. Reference values (Commission of the European Community, CEC, recommendations for patients receiving dialysis):

- Normal = $<10\mu gL^{-1}$ (no history of chronic renal failure; CRF)
- $<60\mu gL^{-1}$ = desirable in CRF patients
- $>60\mu gL^{-1}$ = excessive accumulation
- $>100\mu gL^{-1}$ = cause for concern; high risk of toxicity in children
- $>200\mu gL^{-1}$ = urgent action required; high risk of toxicity in all.

9.5.1.2 Aluminum—Water, Dialysis Fluid

Treatment of CRF by dialysis can give rise to increased aluminum concentration in the patient. Reference values (CEC Recommendations):

- Maximum allowable concentration (MAC) for potable water: $200\mu gL^{-1}$
- Guideline concentration (GLC) for potable water: $50\mu gL^{-1}$
- MAC for water for preparation of dialysis fluid: $30\mu gL^{-1}$.

9.5.1.3 Aluminum—Urine

CEC reference range shows that excretion is usually $<25\mu g/24h$.

9.5.2 Antimony

Antimony exists as V and III valence status with similar chemical characteristics as arsenic. In the geo-environment they occur simultaneously. The daily intake via food is estimated to be around 10μg/day. Exposure to antimony is rare. For biological monitoring concentration in blood and urine is an indicator of exposure and internal dose.

9.5.3 Arsenic

Arsenic is distributed in the Earth's crust with an average concentration of $2mgkg^{-1}$. Rock, soil, water, and air contain trace amounts of arsenic. Arsenic compounds are found in close association with gold as arsenopyrites in mining areas. Wines made from grapes sprayed with arsenic-containing insecticides may also contain high levels of arsenic. The chemistry of arsenic focuses on inorganic forms (−3, 0, +3, and +5) and on organic arsenic compounds of which arsenobetaine occurring in fish is the most prominent one. Inorganic arsenic of geological origin is found in groundwater and used as drinking water it gives rise to adverse health effects in several parts of the world, e.g., in Bangladesh, Hungary, and China.

The development of a variety of instrumental techniques, i.e., atomic absorption spectroscopy (AAS) and inductively coupled plasma mass spectrometry (ICP-MS) with hyphenated methods and element-specific detectors coupled to chromatographic separation techniques makes it possible to study chemical species of arsenic. A test kit that is based on the color reaction of arsine with mercuric bromide allows arsenic to be determined under field conditions, e.g., in the groundwater in Bangladesh with a detection limit of $50–100\mu gL^{-1}$.

Biochemical condition in the geo-environment enhances biotransformation between arsenite and arsenate reduction and methylation of arsenic including organoarsenic compounds. Similar to other cases, biotransformation follows pH. This is an important matter because toxicity of arsenic depends on the chemical species. Acute poisoning occurs when the arsenic blood level is above the normal range of $<10\mu gL^{-1}$ as inorganic arsenic and metabolites. Acceptable occupational exposure (ACGIH value) is $<50\mu gg^{-1}$ creatinine as inorganic arsenic and metabolites.

9.5.4 Cadmium

Cadmium, discovered in 1817, is a soft, silver-white metal and is similar in appearance to zinc. Cadmium does not have a defined taste or odor. Many radioactive isotopes of cadmium, e.g., 109 and 115m, are well recognized in experimental toxicology. Cadmium is an element with an average distribution of $0.1mgkg^{-1}$ in the Earth's crust. Cadmium is usually found associated with zinc. Particularly high concentrations of cadmium occur in some sulfide ores, but many soils, rocks, coal, and mineral fertilizers contain some cadmium. Cadmium is widely dispersed in the environment. Human exposure to low levels occurs as a result of natural processes and of human activities, e.g., mining, smelting, fossil fuel combustion, and industrial use. Due to the natural occurrence in the geo-environment and its active uptake by plants, some farming products such as tobacco could be high in cadmium content. The metal also remains strongly bound to other compounds in the soil and water (WHO 1992a, b).

Cadmium causes kidney damage with proteinuria and calciuria. Bone effects have been reported as itai itai disease in Japan and also as low mineral density of the skeleton in studies from Belgium and China. Cadmium is classified as a human carcinogen (IARC 1994).

A specific environmental exposure to cadmium occurred in Japan. Widespread exposure with both subclinical and clinical effects was found in itai itai patients in areas where water from the Jinzu river was used for irrigation. The cause of this

disease was confirmed to be due to excessive exposure to cadmium through rice. A large number of people living in the cadmium-polluted area have renal tubular dysfunction, and people in other polluted areas have the same health effects. Itai itai disease is characterized by osteomalacia and renal tubular dysfunction and is an unusual disease. The opinion is that cadmium can give rise to both osteomalacia and osteoporosis. The age, sex, nutrition, exercise, and number of pregnancies influences the type of bone effect. The kidney damage can also lead to bone damage. The subclinical bone and renal effects in cadmium-exposed populations may be common and undetected, and could contribute to more severe effects such as fractures and kidney stones.

For biological monitoring of environmental exposure, cadmium is measured in blood and urine. It should be noted that smokers have increased cadmium concentrations by a factor of 2 due to the high content of cadmium in tobacco. The reference range for blood is $<0.2\mu gL^{-1}$ for nonsmokers and $<1.4\mu gL^{-1}$ for smokers. Cadmium concentration in urine for non-smokers is $<1\mu gg^{-1}$ creatinine, and for smokers it is $<3\mu gg^{-1}$ creatinine. The high urinary cadmium may be detected only after renal damage, and by then it may be too late to treat these patients.

9.5.5 Chromium

Trivalent chromium is essential for man and animals, and it plays a role in carbohydrate metabolism as a glucose tolerance factor. The daily chromium requirement for adults is estimated to be 0.5–2μg of absorbable chromium(III). However, this is based on the calculation that if a fractional absorption value of 25% for "biologically incorporated" chromium(III) in food is assumed, then this is provided by a daily dietary intake of 2–8μg of chromium(III). Both acute and chronic toxic effects of chromium are caused by hexavalent compounds that are very toxic.

Ingestion of 1–5g of "chromate" results in severe acute toxic effects such as gastrointestinal disorders, hemorrhagic diathesis, and convulsions. Chromium concentration in serum/plasma and urine has a toxic reference range value in serum/plasma of $<0.5\mu gL^{-1}$ and for urine $<1\mu gg^{-1}$ creatinine.

9.5.6 Cobalt

Cobalt is an essential metal for vitamin B_{12}, which is involved in various methyl transfer reactions. About 25% of cobalt is absorbed from the GI tract, and it is mainly excreted in urine. Addition of cobalt to beer has caused endemic outbreaks of cardiomyopathy among beer drinkers resulting in fatalities.

9.5.7 Copper

In the general environment humans are exposed to copper via food and drinking water. Copper in drinking water has for some time been regarded as the cause of diarrhea and stomach problems in certain countries. Copper is found naturally in a wide variety of mineral salts and organic compounds and in the metallic form. It is essential for all biota. It is widely used in cooking utensils, water distribution systems, and in fertilizers. Bactericides, fungicides, algicides, antifouling paints, and animal feed additives and growth promoters also contain copper. It is also used in a number of industrial applications. Major sources for copper distribution in the environment are mining operations, agriculture, solid waste, and sludge from treatment factories. Copper that is biologically available can accumulate in tissues and give rise to high body burdens in certain animals and terrestrial plants (see also Chaps. 15 and 21, this volume).

The highest concentration of copper for the human diet is found in animal flesh, liver, oysters, fish, whole grains, nuts, seeds, and chocolate. Concentrations of approximately $10mgkg^{-1}$ have been reported. The adult daily intake of copper via food is estimated to be between 1 and 2mg and for children 2years of age it is 0.6–0.8mg. The contribution from drinking water is usually not included in these estimates. Thus the contribution of copper from drinking water can in some cases be high and populations should be alerted.

Also breastfeeding can contribute to an infant's exposure to copper. Concentrations of copper in drinking water exceeding $1–2mgL^{-1}$ give rise to staining of sanitation porcelain. Also hair turns blue-green as described for people exposed to water in, for example, swimming pools. The taste from copper influences the quality of water as reported for water of $0.3–12.7mgL^{-1}$. The taste from copper might be hidden due to the content of other additives of the drink and thus a misleading impression of copper content in water can occur. WHO recommends that the daily essential need for copper is 0.6mg for children from 6months to 6years.

The risks of copper exposure to human health for the general population are through food and drinking water when contaminated with copper. Thus, the major route of excessive copper exposure is oral. In Sweden, most of the water pipeline system consists of copper. Copper pipes were also used in several other countries. Copper is generally thought to be a good material to use for pipeline systems but under certain circumstances copper is released from the pipes, for example, acid rain can increase the bioavailability of copper.

About 30–40% of intake of copper is absorbed in the intestine and transported by albumin to the liver. After hepatic uptake, copper can be incorporated into copper-containing enzymes or into ceruloplasmin, which is then exported into the blood. Copper in the cytoplasm is

predominantly bound to MT, and any excess of copper is excreted into the bile mainly through a lysosome-to-bile pathway, which results in fecal excretion. Normally copper concentration in tissues is regulated by homeostatic control. Under abnormal conditions such as genetic diseases (e.g., Wilson's disease), biliary excretion of copper is impaired and it is accumulated in the liver, which is the critical organ of copper toxicity.

Copper is an essential metal that can be toxic when homeostatic control fails. Adverse health effects of copper can develop both from deficient and excessive intake. Copper deficiency can cause heart diseases. In the general population, copper toxicity occurs due to consumption of contaminated beverages, including drinking water. Copper can catalyze the production of hydroxyradicals and oxyradicals when it is available in Cu^{+}, a redox-active form. Both these radicals are extremely active and can attack many cell constituents, including lipids, nucleic acids, and proteins. Thus the occurrence of apoptotic bodies in the livers of copper-loaded animals is indicative of copper-induced DNA damage.

Special attention should be paid to a sensitive population with genetic disorders such as Menkes' or Wilson's disease. These are two specific inherent genetic disorders that give rise to disturbed copper metabolism. The copper transport protein, P-type ATPase is mutated in Wilson's disease, and copper accumulates in the liver, causing hepatic damage. Menkes' syndrome is characterized by disruption of copper transport from the intestine to the blood, which gives rise to copper deficiency and low activity of copper-dependent enzymes. Increased copper concentration in livers is seen in subjects suffering from Indian liver cirrhosis.

A relationship between MT and copper has been detected in patients with Wilson's disease. Induction of MT in the GI tract by oral zinc administration has been used to treat Wilson's disease by blocking the intestinal uptake of copper and decreasing the toxic tissue accumulation of copper.

MT induction in the intestine by feeding high levels of zinc can decrease copper uptake and tissue concentration. In Wilson's disease, the high hepatic copper is mainly bound to MT. This disease is due to a genetic defect in the transport of Cu into bile. Metallothionein has also been shown to be present in the placenta in patients suffering from Menkes; disease. The cause of Indian liver cirrhosis is still unknown, but high levels of copper have been detected in the liver of these patients.

Another disease is Indian childhood cirrhosis (ICC) reported mainly from India due to cooking utensils that are rich in copper. Nutritional health effects due to low and insufficient copper intake also exist and can affect the heart.

Limit values for health effects are weakly estimated. WHO has a recommended value of copper in drinking water of $2 mgL^{-1}$ based on an assumption that 10% of copper intake originates from drinking water. A provisional tolerable daily intake of copper exists since 1982; however, it is very close to the dose that causes vomiting. Tap water of $0.05 mgL^{-1}$ may be caused by corrosion of pipelines. Concentrations exceeding $0.2 mgL^{-1}$ can cause staining of sanitation porcelain (toilets and bath tubs) and hair. At 10mg copper L^{-1} there is an increased risk for taste and odor. Health effects start to occur at $2 mgL^{-1}$. This concentration increases the risk for diarrhea in children. The practical general recommendation is to allow water to run free from the tap for 1min before using the water for food preparation.

9.5.8 Iodine

In 1990, the United Nations and WHO estimated that about one billion people are at risk for iodine deficiency disorders (IDD), 211 million with goiter (enlargement of the thyroid gland), 5.1 million with severe cognitive and neuromotor deficiencies (cretinism), and many more with less severe neuropsychological defects. The loss of human capital contributes to the perpetuation of poverty and its associated social ills. Therefore, the elimination of IDD is a priority for the WHO (see also Chap. 17, this volume).

Goiter is a recognized disease of great antiquity. Some more recent advances in the understanding of iodine deficiency are listed in Table 9.9. Iodine deficiency may be understood through the context of thyroid function. The normal adult thyroid weighs 20–25g and contains 8–10mg of iodine. Goiter is the earliest and most common manifestation of IDD (Table 9.10).

Features of neurological cretinism include a wide range of mental retardation (nearly normal to severe) with associated hearing and speech disorders—the most severe is deaf-mutism—and abnormal neuromotor functions, e.g., proximal spastic rigidity of muscles of the leg with shuffling gait. Disposition is usually equable—most are able to carry out simple tasks of daily living and primitive farming and may have families and children. Growth is similar to that of the indigenous population, plasma T_4 is normal or low-normal, hypothyroidism is infrequent, and goiter may be present. Myxedematous cretinism is characterized by mental retardation, fetal hypothyroidism, persistent myxedema, growth stunting, and musculoskeletal disorders such as scoliosis, and atrophic thyroid gland. Mixed endemic cretinism is characterized by a combination of the above manifestations. The two types of cretinism may occur in the same endemia. The prevalence of cretinism in IDD endemias is 0–15% with 5–8% common. Factors that determine the prevalence and type of cretinism are incompletely understood. High-dietary goitrogens and selenium deficiency, noted below, have been postulated.

Table 9.9 Some historical advances in knowledge of iodine deficiency

Date	Name	Observation
	Chinese	The ancient Chinese were treating goitre with powdered seaweed and sea urchins several 1,000years ago
BCE	Greeks	Burnt sponge used to treat goiter
1811		The discovery of iodine by adding conc. Sulphuric acid to a seaweed of the type that was used to treat goitre
1819	Fyfe	Iodine identified in sponge
1820	Coindet	Treated goiter with iodine
1854	Chatin	Suggested low iodine in soil, water and food caused goiter
1896	Baumann	Thyroid rich in iodine
1896	Halsted	Maternal thyroid removal caused fetal thyroid hyperplasia (dog)
1908	McCarrison	Endemic cretinism characterized
1909	Marine	Maternal iodine deficiency caused goiter in fetus (dog)
1915	Kendall	Discovery of thyroxin
1917	Smith	Maternal iodine deficiency caused "cretinism" (swine)
1921	Marine	Prevention of goiter by iodide
1927	Harrington	Synthesis of thyroxin
1941	Mackenzie	Sulfanilguanidine inhibits iodide concentration by thyroid (rat)
1943	Mackenzie	Aminobenzene and thiourea inhibit iodine concentration by thyroid (rat)
1943	Mackenzie	Hyperplasia of pituitary gland in hypothyroid state (rat)
1947	Vanderlaan	Thiocyanate inhibits iodide concentration by thyroid (rat)

Table 9.10 Iodine deficiency disorders

Fetus	Malformations	
	Abortion	
	Perinatal death	
	Infant death	
	Neurological cretinism	Severe mental deficiency
		Deaf-mutism
		Spastic diplegia
		Squint
	Myxedematous cretinism	Growth-stunting
		Severe mental deficiency
	Psychomotor deficiency	
Neonate	Goiter	
	Hypothyroidism	
Child & adolescent	Goiter	
	Hypothyroidism	
	Mental deficiency	
	Low physical development	
Adult	Goiter	Mechanical compression of adjacent organs in the neck
		Endocrine disorders: hyperthyroidism; hypothyroidism; Neoplasia: benign tumors; cancer
	Mental deficiency	

The physical finding of goiter suggests the presence of iodine deficiency. Proof is provided by the concentration of iodine in urine. Concentrations $<20\mu gL^{-1}$ are indicative of severe IDD, 20–$49\mu gL^{-1}$ indicates moderate IDD, and 50–$99\mu gL^{-1}$ indicates mild IDD. Concentrations between 100 and $200\mu gL^{-1}$ are satisfactory. Thyroid-stimulating hormone (TSH) concentration in blood plasma reflects iodine nutriture. This test is used to screen newborns for hypothyroidism. In IDD endemic regions such as northern India and Zaire up to 10% of neonates were found to have increased plasma TSH, which implied severe iodine deficiency, hypothyroidism, and a high likelihood of brain damage.

Selenium is required for activity of iodothyronine deiodinase enzymes I–III that deiodinate T_4, T_3, and reverse T_3 and thus regulate the concentration of T_3. Additionally, the selenoproteins glutathione peroxidase and thioredoxin reductase, in concert with glutathione reductase, are believed to protect the thyroid gland from peroxides

produced during the synthesis of T_4 and T_3. When soils are low in selenium as well as iodine, simultaneous deficiencies can occur. This phenomenon apparently occurs in central Africa and western China. It has been speculated that selenium deficiency increases the severity of IDD and contributes to the occurrence of myxedematous cretinism.

Limited data suggest zinc nutriture affects human thyroid function. Zinc deficiency inhibits liver type I 5′-deiodinase, and lowers plasma concentrations of T_3. These effects are expressed physiologically by impaired temperature regulation. Theoretically zinc nutriture also affects the resistance of thyroid tissue to peroxidation through glutathione reductase and thioredoxin reductase. Both are flavoenzymes. Zinc is essential for flavokinase and synthesis of flavin adenine dinucleotide (FAD). Some zinc-deficient humans were found to have low plasma concentrations of T_3 and increased plasma concentrations of reverse T_3. It is possible that some zinc-deficient humans are hypothyroid. Because zinc deficiency is common among the world's poor, many of whom are at risk of iodine deficiency, interactions between low zinc status and iodine deficiency are of more than theoretical interest.

The minimal iodine requirement of adults under usual circumstances is 50–75μg/day. To meet this need and provide a margin of safety the Food and Nutrition Board (FNB), Institute of Medicine, National Academy of Medicine, United States, recommends 150μg/day for both sexes, and more during pregnancy (220μg/day) and lactation (290μg/day).

Diets containing foods of marine origin are rich in iodine. For example, marine fin and shellfish contain 300–3,000μg iodine g^{-1} as contrasted to the 20–40μg iodine g^{-1} in freshwater fish. Fertilizers that contain marine products can increase the iodine content of plants 10- to 100-fold, and iodine-enriched rations can increase the iodine in eggs and milk 100- to 1,000-fold.

Iodine in soil and water determines the iodine content of foods (see also Chap. 17, this volume). For example, in England the average daily intake of iodine is about 220μg. Similarly in the northeast United States average intakes are about 240μg. In contrast, intakes in the southwest United States are about 740μg. In Japan daily intakes are about 300μg, when little seaweed is eaten. Seaweed consumption can increase iodine intakes to 10mg daily. Approximate iodine contents of American foods are listed in Table 9.11. Of note is the wide variability. Foods raised on iodine-depleted soil are poor sources of iodine.

Prevention of primary iodine dietary deficiency requires the administration of iodine. Iodine enrichment of foods commonly consumed by the population at risk is the preferred approach. Salt is the most common vehicle. Salt iodization with KI or KIO4 is used in some areas and where used it is economical and efficacious. However, salt iodization may not be effective when customs or economic reasons cause the population to obtain salt from traditional small producers and distributors, and not from large producers equipped for iodization. In addition, iodine enrichment of salt has no effect on populations that use little or no salt. A second approach is the addition of iodine to bread. Wide variation in bread consumption and the preparation of bread in the home and small bakeries can detract from this approach. The addition of iodine to water supplies has been used in some settings. The small amount of iodized water consumed is a major limitation. When these approaches are not practical, oral administration of iodine-containing tablets, oil, or confections have been used, or iodine-containing oil has been injected. An obvious limitation of these approaches is the need for continuous cooperation by the recipients and the people responsible for delivery of the iodine. Even so, every 3years intramuscular injection of iodized oil given to women of child-bearing age has eliminated cretinism in some regions. In addition, the Chinese have used irrigation of crops with iodine-enriched water.

Table 9.11 Approximate iodine content of foods (U.S.)

	Iodine (μg/g w.w.)	
Food class	Mean ± SEM	Number of samples
Fruit	40 ± 20	18
Bread/cereals	100 ± 20	18
Dairy	130 ± 10	18
Eggs	260 ± 80	11
Meat	260 ± 70	12
Vegetables	320 ± 100	13
Marine	660 ± 180	7

9.5.9 Iron

Iron is an essential element in human nutrition but it can be toxic. Estimates of the minimum daily requirement of iron for humans depend on age, sex, physiological status, and iron bioavailability. The range is 10–18mg/day, 30mg/day if pregnant (U. S. recommended daily allowance; RDA), and 14mg/day (EU RDA).

Iron toxicity can occur at high levels of intake. The average lethal dose of iron is 200–250mgkg^{-1} of body weight. However, even an oral intake as low as 40mgkg^{-1} of body weight has been lethal. Chronic iron overload results primarily from a genetic disorder (hemochromatosis) characterized by increased iron absorption and from diseases that require frequent transfusions. Intake of 0.4–1mgkg^{-1} of body weight per day is unlikely to cause adverse effects in healthy people.

Iron deficiency, probably the most common nutritional deficiency, is believed by some authorities to affect 80% of the world's population, or about five billion people, two billion of whom are anemic. Especially at risk are young children and premenopausal women, both pregnant and non-pregnant. Low socioeconomic status (SES), high dietary phytate, and other inhibitors of iron bioavailability and low consumption of flesh foods and chronic blood loss increase the risk of deficiency. Knowledge of iron deficiency and its effects has a long and rich history. Examples of advances in understanding iron in human nutrition are listed in Table 9.12.

Iron deficiency exists when body iron stores are completely depleted and iron-dependent processes malfunction. Iron deficiency may be associated with many abnormalities (Table 9.13). However, because iron deficiency related to diet seldom occurs alone and is usually part of a syndrome of micronutrient deficiencies, a cause-and-effect relationship between iron status and some clinical phenomena is obscure or nonexistent. Controlled experiments in other species have clarified these issues (Table 9.14).

Iron deficiency related to diet and/or chronic blood loss evolves slowly. Initially iron stores are depleted and iron is less available for iron-dependent biochemical functions. This is reflected by decreased synthesis of heme, and the activity of cytochrome enzymes, aconitase, and other iron-sulfur enzymes is decreased. Iron-depleted aconitase (three irons) in intestinal mucosa, whose concentration is effected by iron in plasma, mediates mechanisms that increase intestinal iron absorption. These cellular effects occur when iron stores are depleted and before hemoglobin concentration is significantly decreased. More than half of iron-deficient people have this type of iron deficiency. Most affected individuals are unaware of its morbidity. Research data indicate that abnormalities in cold intolerance, muscle endurance, immunity, and neuro-psychological function can be detected. Other associated micronutrient deficiencies depend on the type of diet consumed. For example, diets that exclude red meat increase the likelihood of both iron and zinc deficiencies in young women who menstruate regularly.

Iron deficiency anemia occurs after all chemical indicators of deficiency are abnormal. Anemia is relatively mild in most individuals and is poorly related to symptoms or awareness of morbidity. When anemia is more severe other manifestations of the deficiency syndrome are more evident. For example, the anemia may become a "mixed anemia" as deficiencies of other micronutrients such as copper, pyridoxine, retinol, zinc, and folate become manifest. When this occurs treatment with iron alone will not fully restore erythropoiesis to normal. Other examples of conditions that may in part be caused by iron deficiency, but are also caused by associated deficiencies, include stunted growth and delayed sexual development, low immunity, impaired neuropsychological function, and abnormal pregnancy outcomes. In addition, research in animal models suggests that some clinical signs involving epithelia (skin, hair, nails, mouth, tongue, esophagus, stomach, and duodenum) that may be associated with iron deficiency are probably caused by associated micronutrient deficiencies, e.g., zinc, pyridoxine, and riboflavin.

Iron deficiency occurs when the diet provides insufficient bioavailable iron. Bleeding is a conditioning factor. Body iron content is regulated by feedback through aconitase-mediated control of iron absorption. With the exception of surface and menstrual losses, iron is reutilized.

Basal iron losses from the exterior and interior surfaces of men are about $14\mu g kg^{-1} day^{-1}$, an amount of iron readily available from usual "western" diets. Under usual circumstances premenopausal women are at risk of iron deficiency because their non-menstrual iron losses are similar to those of men, and they lose about 6–179mL of blood monthly (intrauterine devices can cause substantially greater losses). About 10% of normal women lose >80mL of blood monthly. Thus the iron needs of some women for maintenance are 2.84mg iron per day (95th percentile). Therefore women, who absorb 15% of iron when iron stores are low, must consume about 18.9mg of food iron daily to be assured of adequate iron status. This is difficult to do. Consequently, a national survey in the United States found that the 25th percentile for serum ferritin of premenopausal women was $14\mu g L^{-1}$, which suggested one out of four American premenopausal women is iron deficient by the criteria of absent iron stores.

Newborns generally have adequate iron stores for the first 4–6months of life. They then become an increased risk of iron deficiency up to 2years of age because of the low bioavailability of iron from common cereal-based weaning foods and high growth rate. Their iron requirements are about $100\mu g kg^{-1} day^{-1}$, or four times the average needs of menstruating women. Later, after age 2, growth of children slows and requirements decrease. Adolescents who are growing rapidly have iron requirements of about 20% (boys) and 30% (girls) more, respectively, than the needs of menstruating women. The requirements of girls are related to the combined effects of growth and menses.

Pregnancy and lactation substantially increase maternal iron requirements (Table 9.15). Multiple pregnancies without repletion of iron nutriture can result in severe iron deficiency. This phenomenon is especially common in societies where diets are based on unrefined cereals and legumes and flesh foods are infrequently eaten.

Bioavailability is a critical factor affecting iron adequacy. Most food iron (non-heme iron) is bound to proteins and

Table 9.12 Advances in understanding of iron in human nutrition

Date	Name	Observation
1554	Lange	Chlorosis: greenish palor and languor in young women
1661	Dr. Sydenham's practice of physick	Iron treatment for chlorosis
1713	Lemery	Iron present in blood
1832	Foedisch	Low iron content in blood of chlorotics
1832	Blaud	Ferrous sulfate efficacious for chlorosis
1846	Magendi	Dietary iron increased blood iron of experimental animals
1895	Stockman	Dietary iron of men and women, and relation to chlorosis
1897	Cloetta	Dietary iron prevented "milk anemia" in dogs
1910	Dock	Hookworm associated with growth stunting
1919	International Health Board	Hookworm associated with low intellectual performance in children and young adults
1919	Waite	Hookworm associated with retarded mental development
1925	Whipple	Iron and unidentified nutrients essential for erythropoesis
1925	Keilin	Cytochrome enzymes discovered
1927	Hart	Copper essential for iron intestinal absorption
1928	Mackay	Iron treatment of infants decreased morbidity from respiratory and gastrointestinal infections
1933	Strauss	Infants born to iron deficient women at risk of deficiency
1936	Bernhardt	Low maze learning in post-weaning rats
1943	McCance	Dietary phytate impairs iron absorption
1943	Hahn	Mucosal block theory of iron absorption
1963	Prasad	Iron and zinc deficiencies occur together
1966	Oski	Ceruloplasmin oxidizes Fe^{+2} to Fe^{+3} for binding to transferrin
1967	Sandstead	Zinc deficiency, not iron deficiency causes growth stunting
1968	Lee	Copper essential for utilization of tissue iron
1973	Webb	Low academic achievement in adolescents
1974	Cantwell	Residual neurological abnormalities in children after iron deficiency as an infant
1978	Oski	Mental development of iron deficient infants improved by iron

Table 9.13 Examples of chemical effects of iron deficiency on cells

Type	Effect
Heme proteins	Hemoglobin and myoglobin: low
	Cytochromes – cytochrome-C: low in skeletal muscle, liver, intestine, kidney; but little or no change in brain and heart
	Catalase: low in erythrocytes
Metalloflavoproteins	Monoamine oxidase: low in liver and platelets
	Aldehyde oxidase: low in brain mitochondria
	Alpha-glycerophosphate dehydrogenase: low in skeletal muscle
	Succinate dehydrogenase: low in heart and kidney
	Xanthene oxidase: low in heart and kidney
Cofactors	Aconitase: low in kidney and liver; activity in intestinal mucosa directly correlated with iron stores and inversely with iron absorption
	Protocollagen-proline hydroxylase: low
Nucleic acid metabolism	Ribonucleotide reductase: low

other food constituents and is usually about 1–5% bioavailable. In iron-deficient individuals feedback stimulation may increase absorption of non-heme iron as much as 20% if substances that bind iron and inhibit absorption are absent and facilitators are present. Flesh foods provide iron-protoporphyrin (heme iron) that is 15–35% bioavailable. Red meat is the best source in that nearly 50% of its iron is heme iron. Non-red-flesh foods contain less heme iron. The iron content of foods can be retrieved at Web sites of national agencies.

Dietary non-heme iron is in the ferric state (Fe^{+3}). Organic acids reduce ferric iron to the ferrous state (Fe^{+2}), the form in which most iron is absorbed. Absorption of ferrous iron occurs primarily in the duodenum. Nondigestible substances including phytate (hexaphosphate-inositol), certain dietary fibers, lignins, phenolic polymers, oxalate, products of

Table 9.14 Clinical abnormalities described as associated with iron deficiency in humans

Skin	Poor growth of hair
	Dry and fissured
	Infections
	Spoon shaped deformity of nails (koilonychia)
Nose	Atrophy of mucosa (ozena)
Mouth	Bilateral angular stomatitis
	Atrophy of mucosa
Tongue	Atrophy of mucosa with loss of papillae
Esophagus	Dysphagia from hyperplasia of basal cells and perakeratosis of surface cells causing a web-shaped constriction of the mucosa just below the cricoid cartilage, known as Plummer Vinson Syndrome
Gastric mucosa	Atrophy, achlorohydria, and low intrinsic factor secretion
Intestinal mucosa	Atrophy of duodenal mucosa
	Iron absorption regulated by iron depleted aconitase: increased
Liver	Reticuloendothelial cell iron: absent
Spleen	Reticuloendothelial cell iron: absent
Immune system	Morbidity from infections: increased or decreased (depends on agent)
	Circulating immunoglobulins: no change or increased
	Circulating T cells: decreased
	Lymphocyte subsets: decreased
	Lymphocyte proliferation *in vitro*: decreased, increased or unchanged
	Skin hypersensitivity to antigens: decreased
	Phagocyte function: decreased
Bone marrow	Iron: decreased to absent
	Hemoglobin synthesis: decreased
	Erythropoesis: increased
	Intermedullary hemolysis: increased
Erythrocytes	Normochromic normocytic anemia (early in deficiency)
	Hypochromic microcytic anemia
	Erythrocyte survival: decreased
	Zinc protoporphyin concentration: increased
	Transferrin receptors: increased
Blood plasma	Iron in ferritin: decreased
	Ferritin protein: decreased when acute-phase stimuli are absent
	Serum iron: decreased
	Transferrin concentration: increased
	Iron bound to transferrin: decreased
	T_4 concentrations: decreased
	Catacholamine concentrations: increased
Muscle	Exercise endurance: decreased
	Physical work productivity: decreased
	Myoglobin synthesis: decreased
Brain	Neuropsychological function: decreased
	Pica (perverse appetite: craving for and compulsive ingestion of food and non-food items)
	Affective behaviors: inconsistent symptoms, e.g., fatigue, weakness, headache, irritability, depression
Growth	Stunted
Maturation	Retarded
Fetus	Perinatal death increased; poorly reversible retarded development
Maternal status	Maternal death increased

Maillard browning, and alkaline clays bind ferrous iron and inhibit its absorption. Calcium inhibits absorption of both non-heme and heme iron. Facilitators of non-heme-iron absorption include cysteine from meat, ascorbic acid, and other organic acids.

Diets low in heme iron and facilitators of non-heme-iron absorption greatly increase the risk of iron deficiency. Such diets are common in nonindustrialized countries where poverty and/or customs limit consumption of flesh foods and cereals and legumes are the principal sources of protein. In

Table 9.15 Iron requirements of pregnancy and lactation

	Iron (mg)
Fetus	200–300
Placenta and cord	30–170
Blood lost at delivery	90–310
Maternal milk (6months)	100–180
Total	420–1,030
Daily need: gestation and 6months lactation	1–2.5

Table 9.16 Iron available to infants from human milk and cow milk preparations

Source	mgL^{-1}	% Bioavailable	Absorbed (mgL^{-1})
Breast milk	0.5	~50	0.25
Whole cow's milk	0.5	~10	0.05
Non-fortified formula	1.5–4.8[a]	~10	0.15–0.48
Iron-fortified formula[b]	10–12.8[a]	~4	0.40–0.51

[a]Common infant formulas in the USA
[b]Iron-fortified formula contains 1mg iron/100kcal formula; most iron-fortified formulas contain $680kcalL^{-1}$, equivalent to 6.8mg iron L^{-1}

developed countries food choice is an important determinant of the occurrence of dietary iron deficiency. Clay eating, a culturally determined "dietary" practice is the cause of iron deficiency in some populations.

Breast milk is adequate in iron until about 6months postpartum. Non-human milk, e.g., cows' and goats' milk, contains very little bioavailable iron. Thus infants weaned early to non-human milk are at risk for iron deficiency. Weaning foods based on cereals that are rich in phytate increases the risk of deficiency, as do formulas prepared from phytate-rich soy products. Modern iron-fortified, processed cows' milk formulas that provide 1mg iron/100kcal substantially decrease the risk of iron deficiency. A comparison between breast milk and cows' milk preparations is seen in Table 9.16.

Empirical practice suggests that iron-fortified cereals are the first foods fed infants at weaning. Recent research suggests infants also accept and tolerate weaning foods prepared from animal products rich in heme and sulfur amino acids. This innovation needs further evaluation.

Chronic blood loss is the second major cause of iron deficiency, and hookworm is the primary agent responsible. Hookworm afflicts at least two billion people. *Ancylostoma duodenale* affects the Middle East, North Africa, and southern Europe, whereas *Necator americanus* predominates in the Americas and Australia, and both also occur in central and southern Africa. The disease is endemic where the climate is warm and moist and sanitation is rudimentary. Adult worms suck blood from the mucosa of the small intestine and disperse their eggs in human feces. If dropped on appropriate soil larva mature to the filariform stage which can penetrate the skin (feet and legs are the usual points of entry) and migrate to the small intestine where they transform into adults.

9.5.10 Lead

Lead occurs in ore and soil as both inorganic and organic compounds with different types of toxicity to humans. Lead has been used in paint, in ceramics, and in home utensils. The main exposure route is via food and drinking water. It can cause neurotoxic effects in children. An early effect in adults is the interference with the hemoglobin syntheses with an increase of eryth-rocyte zinc protoporphyrin (ZPP) in whole blood. ZPP is sometimes monitored in whole blood as an indicator of lead exposure. This can also be seen in iron-deficiency anemia. Humans suffering from intermittent protoporphyria are considered a vulnerable group for lead toxicity.

In acute and chronic poisoning from environmental exposure to inorganic Pb the reference range in blood for adults is usually $<100\mu gPbL^{-1}$. For children, the levels should not exceed $40\mu gPbL^{-1}$ because of its neurotoxic effects.

The metabolism and distribution of organic Pb differs markedly from the inorganic form, and urine is used as the medium for biological monitoring. Monitoring of inorganic Pb in urine is only recommended during chelation therapy. After the removal of tetraethyl lead from gas, the concentration of lead in blood in children has markedly decreased.

9.5.11 Manganese

Manganese is an essential trace element with an estimated daily nutritional requirement of $30–50\mu gkg^{-1}$ of body weight. Manganese is required for several enzymes involved in carbohydrate metabolism. Absorption rate is influenced by actual intake, chemical form, and the presence of other metals, such as iron and copper, in the diet. In infants and young animals very high absorption rates of manganese have been observed.

The biological half-time of manganese in humans has been determined to be about 12–35days, depending on the nutritional status. The major route of excretion of manganese is through the biliary system, and a low tissue level is maintained by this mechanism. Because of its chemical similarity to iron, manganese also binds to iron-binding proteins such as transferrin. Interactions between manganese, iron, and lead have been shown in rats (Malhotra et al. 1984). Although manganese is not very toxic, its increased tissue accumulation can cause toxic effects in the brain and lung.

Excessive absorption of manganese from lungs can increase its accumulation in the brain. Brain damage has been reported in miners exposed to manganese dioxide dust, and it can progress to irreversible brain injury similar

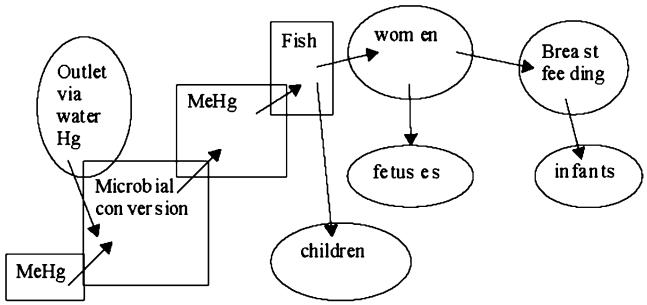

Fig. 9.3 Mercury exposure via the nutritional chain with vulnerable groups indicated in bold

to Parkinson's disease. The most important biochemical effects of manganese are on the metabolism of various neurotransmitter substances such as dopamine. The selective injury of catecholamine neurons by manganese is similar to 6-hydroxydopamine-induced neuronal injury, and it may be related to a generation of toxic free radicals. Certain manganese compounds such as manganese carbonyl compounds have been used as anti-knocking agents to replace lead in several countries. The long-term effects of these compounds on people, especially the elderly, should be monitored because of its known effects on catecholamines in brain and its relation to Parkinson's disease. The interactions of other metals on the neurotoxicity of manganese should also be studied to understand the mechanisms involved in metal-induced neurotoxicity.

9.5.12 Mercury

Mercury is found mainly in food, especially fish as methylmercury, and it is the major source of mercury exposure in various parts of the world. Exposure to mercury gives rise to adverse health effects such as neurobehavioral disorders and is an issue of public health concern. Cognitive impairment in children, following exposure of methylmercury during pregnancy, has been reported from several epidemiological studies from New Zealand (Kjellström et al. 1986), from the Seychelles (Clarkson 1997), and from the Faroe islands (Grandjean et al. 1997). The message of public health concern is that women of child-bearing age should not consume species containing methylmercury (Fig. 9.3).

The major source of exposure to mercury vapor in the general population is from dental amalgam fillings. Dental amalgam consists of about 50% mercury along with other metals such as silver and copper. They have been used widely for the last 150years because they are long lasting, inexpensive, and easier to use than other types of dental fillings. There are reports of mercury poisoning in dentists and dental technicians who handle amalgam as well as reports of side effects in patients. However, the use of amalgam in dental practice has been controversial because of the assumed toxic effects of mercury. It is known that amalgams can release mercury vapor into the oral cavity and if inhaled up to 80% is absorbed in the lungs. What is absorbed is transported to the bloodstream and part of it may enter the CNS through the blood–brain barrier, but a great part of it may be excreted in the urine. Normally the absorbed mercury vapor is excreted in the urine. About 80% of inhaled mercury vapor is taken up. The normal mercury level in urine is less than $0.05 mgL^{-1}$, and the maximum allowable level is $0.15 mgL^{-1}$. The threshold limit value (TLV) for mercury vapor is $0.05 mgm^{3-1}$, and is calculated for a working schedule of 8h/day and 40h/week.

9.5.12.1 Mercury—Blood

The blood level of mercury is a useful indicator for both acute and chronic exposure to organic mercury compounds; but it may be of limited use for acute exposure to vapor or inorganic salts. Reference range is $<4 \mu gL^{-1}$.

9.5.12.2 Mercury—Urine

Urinary levels of mercury are useful to measure exposure to mercury vapor and to inorganic mercury salts. Analysis of mercury in urine has been recommended for people concerned about its release from dental fillings. Reference range: excretion usually $<10 \mu g/g$ creatinine/$<10 \mu g/24h$.

According to the IPCS/WHO Health Criteria Document on inorganic mercury (1991), when mercury vapor exposure is above $80 \mu gm^{3-1}$, $25–80 \mu gm^{-3}$ corresponding to a urinary mercury level of $100 \mu g/g$ creatinine, the probability of developing the classical neurological signs of mercury intoxication such as tremor, erethism, and proteinuria is high. Exposure to mercury vapor in the range of $25–80 \mu gm^{3-1}$, corresponding to urinary level of 30–100μg mercury/g of creatinine can lead to increases in the incidence of certain less severe toxic effects.

9.5.13 Molybdenum

Molybdenum is considered to be an essential trace element in both animals and humans. Safe and adequate intake levels suggested for the population are 0.015–0.04mg/day for infants, for children of age 1–10 the level is $0.025–0.15 mgday^{-1}$, and $0.075–0.25 mgday^{-1}$ for humans over 10years of age.

A disease of Swedish moose is explained by interference of molybdenum with copper; see Chap. 21.

9.5.14 Selenium

Selenium is an essential trace element. Recent studies have indicated that selenium exerts a beneficial effect on coronary disease mortality, and that selenium plus garlic produces significant anticancer activity. In the Scandinavian countries the intake of selenium is low due to the fact that the soils are poor in

selenium. Also, due to acid rain selenium has less bioavailability. Depending on the soil content selenium concentration varies in grain. Countries like New Zealand, Finland, and Sweden, with a low concentration of selenium in soils, report intakes below 70μg/day and from China low intakes are reported as below 20μg/day. High concentrations are reported from Scotland, Venezuela, and from certain parts of China of up to 200–700μg/day (see also Chap. 16, this volume).

An estimated daily intake in Sweden is about 24–35μg. A recommended daily intake in the United States is 55μg for ages 19 and older. For pregnant women the recommended daily intake is 60μg and during lactation the recommended rate is 70μg. In some areas this dose is exceeded. Deficiency occurs when the daily intake is 10μg. Toxicity occurs at intakes of 500μg/day. Health effects related to deficient intake, which occurs at daily intake below 20–30μg occur in muscles and the heart. At high intakes above 1,000μg gastrointestinal irritation, hair loss, and nerve damage occur. Acute exposure may give rise to liver damage. Reported increased incidence of asthma in populations in New Zealand is associated with low selenium intakes.

Selenium deficiency gives rise to heart diseases like Keshan disease, which is most frequently seen in children. Another disease associated with selenium deficiency is Kashin-Beck. Cancer is connected to selenium and influences diseases of the muscles and joints and rheumatics and senility. High intakes of selenium influence the occurrence of caries, the garlic smell of breath, and the blue staining of nails. Selenium intoxication of cattle has been treated with arsenic supplement.

A selenium level in serum between 60 and 120μgL^{-1} reflects sufficient intake of selenium via food. Selenium concentration in hair exceeding 5μgg^{-1} reflects selenium poisoning. Selenium in plasma/serum is measured upon indications of deficiency and/or toxicity and can measure recent (months) changes in intake of or exposure to selenium. In humans the activity of the Se-dependent enzyme glutathione peroxidase is of interest. Reported reference values for neonates to 16years of age are 30–115μgL^{-1} and are age dependent and for adults ranging from 70 to 130μgL^{-1}.

9.5.15 Thallium

Thallium (Tl), is a soft metal and the oxidation states are I and III. The salts are highly toxic. Environmental samples contain μgkg^{-1} or less. However, the determination level for minerals is 20μgkg^{-1} and for aqueous solutions it is about 0.1μgL^{-1}. Thallium can be found in phyllosilicates and in sulfide deposits.

Bioavailability of thallium increases when pH decreases in soil. Thallium can also be leached to ground and surface water. It has a strong tendency to accumulate in aquatic life and plants can easily take up the element by the roots.

Oral intake of (Tl1) 20–60mg thallium kg^{-1} body weight is lethal within 1week. Thallium(III) oxide, which is water soluble, shows a somewhat lower acute toxicity compared to thallium(I) salts. The U. S. Environmental Protection Agency (EPA) suggests that drinking water exceeding action levels can lead to gastrointestinal irritation and nerve damage in the short term, and to changes in blood chemistry, damage to liver, kidney, intestinal, and testicular tissues and hair loss in the long term.

The major symptoms of acute intoxication are anorexia, vomiting, depression, and hair loss. Respiratory failure is lethal. The same symptoms are reported for chronic intoxication. Loss of hair is a typical sign of intoxication caused by thallium. The reference range for acute and chronic poisoning for blood is $<1\mu gL^{-1}$ and for urine $<1\mu gL^{-1}$.

9.5.16 Zinc

Zinc (Zn) is an essential trace element found in all food and potable water as salt or an organic complex. The principal source of zinc is normally the diet. Zinc in surface and groundwater usually does not exceed 0.01 and 0.05mgL^{-1}, respectively, and concentrations in tap water can be much higher as a result of dissolution of zinc from pipes. A daily dietary requirement of zinc of 0.3$mgkg^{-1}$ of body weight was proposed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1982. At the same time JECFA also sug-gested that the provisional maximum tolerable daily intake for zinc is 1$mgkg^{-1}$ of body weight. The dietary reference values for adults range from 6 to 15mg/day. Drinking-water containing zinc at levels above 3mgL^{-1} may not be acceptable to consumers.

Zinc deficiency occurs in human beings when intake is low. This depends on the intake of diets that are low in readily bioavailable zinc. Unrefined cereals are rich in phytate and dietary fibers which all bind zinc and prohibit the bioavailability of the metal. This means that even if food is high in zinc content the intake can give rise to deficiency. This has been described as a public health problem in certain countries such as Egypt.

Zinc in serum is measured upon indications of deficiency. Another way of finding out zinc status is simply by asking about number of meals with red meat per week. This can provide a crude estimate as to whether zinc deficiency should be suspected.

9.5.16.1 Zinc Deficiency

History

Examples of advances in understanding of the nutritional role of zinc are given in Table 9.17. Reference values for zinc status are that $<0.5mgL^{-1}$ may indicate zinc deficiency and 0.5–0.7mgL^{-1} might be of no clinical significance. The "normal" range for all ages is regarded to be 0.7–1.6mgL^{-1}

Table 9.17 Advances in understanding of the nutritional role of zinc

Date	Name	Observation
1869	Raulin	Essential for *Aspergillus niger*
1887	Lechartier	Presence in living tissues
1905	Mendel	Constituent of respiratory pigment of the snail *Sycotypus*
1910	Mazé	Growth factor for maize
1919	Birckner	Proposed "nutritive function" from its "constant occurrence" in human and cow milk
1926	Somner	Essential for higher green plants (sunflower, barley)
1927	Hubbell	Improves growth of mouse
1934	Todd	Deficiency stops growth and causes alopecia (rat)
1941	Follis	Deficiency causes dermatitis with acanthosis, parakeratosis and inflammation; and parakeratosis and basal cell hyperplasia of esophagus (rat)
1952	Mawson	Deficiency causes atrophy of testicular germinal epithelium, epididymes and prostate (rat)
1955	Tucker	Deficiency causes stunting, dermatitis with parakeratosis, diarrhea and death (swine)
1956	Vallee	Possible zinc deficiency in humans with alcoholic cirrhosis
1958	O'Dell	Deficiency in *Aves* causes dermatitis, and retards feathering, osteogenesis and lymphoid tissue
1959	Winder	Facilitates DNA, RNA and protein synthesis of *M smegmatis*
1960	Blamberg	Deficiency is teratogenic (chicks)
1961	Prasad	Deficiency thought to cause stunting and hypogonadism in teenage Iranian farmers
1962	Lieberman	Facilitates DNA synthesis in cultured mammalian cells
1962	Miller	Deficiency in calf has effects similar to those in swine
1963	Prasad	Stunted teenage farmers in Egypt have zinc metabolism consistent with zinc deficiency
1963	Sandstead	Zinc treatment improved growth and development of stunted teenage farmers in Egypt
1964	Ott	Deficiency in lambs has effects similar to those in swine
1966	Hurley	Deficiency teratogenic for rat

whereas $>1.6 mgL^{-1}$ might reflect the use of dietary supplements.

Zinc in urine is measured upon indications and metabolic studies or for chelation therapy. It is, however, of little value in assessing deficiency. This analysis may be of value in monitoring the effect on zinc body burden of long-term chelation therapy of other trace elements. The reference value for excretion is usually 0.3–0.6mg/24h.

9.6 Summary

To understand the full context of the relationship of trace elements to the geo-environment, it is important to encourage interdisciplinary research and to coordinate the knowledge obtained from various scientific fields. This approach may provide a better understanding of the mechanisms involved in both nutritional deficiency and toxicity of trace elements and metals. The nutritional deficiencies can arise from lack of the essential elements in the drinking water or food. This can be due to lack of these elements in the soil where the food is grown or can be due to the eating habits of the people. Certain genetic defects can also affect the absorption or transport of the elements to required tissues. Toxicity might occur when high concentrations of metals in soil and drinking water lead to high exposure to metals. The potential risk of developing toxicity depends on the bioavailability of the specific trace element. These influencing factors are shown in Table 9.18.

Table 9.18 Factors influencing relationship for trace elements and health effects

Eco – and biological system related to exposure, dose and effect;
Environmental exposure in the ecosystem
Environmental and biological monitoring
Acidification and species of metals and trace elements
Bioavailability, species and exposure conditions and toxicity of metals
Metals, geo-environment and environmental biochemistry
Metabolism and kinetics of trace elements
Importance of various proteins such as metallothionein for binding of elements

See also the Following Chapters. Chapter 5 (Uptake of Elements from a Chemical Point of View) • Chapter 6 (Uptake of Elements from a Biological Point of View) • Chapter 7 (Biological Functions of the Elements) • Chapter 8 (Geological Impacts on Nutrition) • Chapter 22 (The Impact of Micronutrient Deficiencies in Agricultural Soils and Crops on the Nutritional Health of Humans)

Further Reading

Bremner I (1987) Nutritional and physiological significance of metallothionein. In: Kägi JHR, Kojima Y (eds) Metallothionein II. Birkhauser Verlag, Basel, pp 81–107

Cherian MG (1995) Metallothionein and its interaction with metals. In: Goyer RA, Cherian MG (eds) Toxicology of metals. Springer, Berlin, pp 121–132

Cherian MG (1997) Metallothionein and intracellular sequestration of metals. In: Sipes IG, McQueen CA, Gandolfi AJ (eds) Comprehensive toxicology, vol 3. Pergamon, Oxford, pp 489–500
Cherian MG, Nordberg M (1983) Cellular adaptation in metal Toxicology and metallothionen Toxicology 28:1–15
Clarkson TW (1997) The toxicology of mercury. Crit Rev Crit Lab Sci 34(4):369–403
Clarkson TW, Friberg L, Nordberg GF, Sager PR (eds) (1988) Biological monitoring of toxic metals. Plenum Press, New York
DelRazo LM, Quintanilla-Vega B, Brambila-Colombres E, Calderon-Aranda ES, Manno M, Albores A (2001) Stress proteins induced by arsenic. Toxicol Appl Pharmacol 177:132–148
Flanagan PR, McLellan JS, Haist J, Cherian MG, Chamberlain MJ, Valberg LS (1978) Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 74:841–846
Goering PL, Fisher BR (1995) Metals and stress proteins. In: Goyer RA, Cherian MG (eds) Toxicology of metals. Springer, Berlin, pp 229–266
Goyer RA, Cherian MG (1978) Metallothioneins and their role in the metabolism and toxicity of metals. Life Sci 23:1–10
Grandjean P, Weihe P, White RF (1997) Cognitive deficit in 7-year-old children with prenatal exposureto methylmercury. Neurotoxicol Teratol 19(6):417–428
IARC (1980) Some metals and metallic compounds, vol 23. IARC, Lyon
IARC (1990) Chromium, nickel and welding, vol 49. IARC, Lyon
IARC (1994) Beryllium, cadmium, mercury and exposures in the glass manufacturing industry monograph, vol 58. IARC, Lyon
Kägi JHR, Nordberg M (eds) (1979) Metallothionein. Birkhauser Verlag, Basel, pp 1–378
Kjellstrom T, Kennedy P, Wallis S, Mantell C (1986) Physical and mental development of children with prenatal exposure to mercury from fish. National Swedish Environmental Protection Board Report 3080, Stockholm, Sweden
Malhotra KM, Murthy RC, Srivastrava RS, Chandra SV (1984) Concurrent exposure of lead and manganese to iron-deficient rats: effect of lipid peroxidation and contents of some metals in the brain. J Appl Toxicol 4:22–30
Nordberg M (1998) Metallothioneins: historical review and state of knowledge. Talanta 46:243–254
Nordberg M, Nordberg GF (2000) Toxicological aspects of metallothionein. Cell Mol Biol 46(2):451–463
Nordberg M, Nordberg GF (2002) Cadmium. In: Sarkar B (ed) Handbook of heavy metals in the environment. Marcel Dekker, Inc., New York, pp 231–269
Piscator M (1964) On cadmium in normal human kidneys together with a report on the isolation of metallothionein from livers of cadmium-exposed rabbits. Nord Hyg Tidskv 48:76
Radtke F, Heuchel R, Georgiev O, Hergersberg M, Garglio M, Dembic Z, Schaffner W (1993) Cloned transcription factor MTF-1 activates the mouse metallothionein 1 promoter. EMBO J 12:1355–1362
Robertson A, Morrison JN, Woods AM, Bremner I (1989) Effects of iron deficiency on metallothionein-1 concentrations in blood and tissues of rats. J Nutr 119:439–445
Seguin C (1991) A nuclear factor requires Zn^{2+} to bind a regulatory MRE element of the mouse gene encoding metallothionein-1. Gene 97:295–300

WHO/IPCS Environmental Health Criteria Documents for Various Metals

WHO/IPCS (1991) Environmental health criteria document 118 inorganic mercury. WHO, Geneva
WHO/IPCS (1992a) Environmental health criteria document 134 cadmium. WHO, Geneva
WHO/IPCS (1992b) Environmental health criteria document 182 thallium. WHO, Geneva
WHO/IPCS (2001a) Environmental health criteria document 224 arsenic, 2nd edn. WHO, Geneva
WHO/IPCS (2001b) Environmental health criteria document 221 zinc. WHO, Geneva
WHO/IPCS (2002) Environmental health criteria document 228 principles and methods for the assessment of risk from essential trace elements. WHO, Geneva