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Abstract

Potentially harmful elements, or more generally trace elements, are now considered to be among the most effective environmental contaminants, and their release into the environment is increasing since the last decades. Metals released by different sources, both natural and anthropic, can be dispersed in the environment and accumulated in plants and, ultimately, in human body, causing serious health problems as intoxication, neurological disturbances and also cancer. Widespread interest in trace elements has risen as major scientific topic only over the last 50 years, when it was realized that some elements were essential to human health (e.g. Fe, Cu, Zn), whereas some others were toxic (e.g. As, Hg, Pb), and likely responsible for serious human diseases, with frequent lethal consequences.

Since that time, great progresses in knowledge of links between environmental geochemistry and human health have been achieved, in combination with epidemiology.

The effects of most trace metals on human health are not yet fully understood, partly because of the interactions between them, and partly because of the complex metabolic reactions in the human body. Despite the copious research addressed to this topic, there is still a paucity of quantitative information on the relations between elements in soils and

human health. Much is known about the functions of most elements in human body, but there is increasing evidence that the interactions among them are more complex than originally thought. Uncertainty is still prevailing, particularly with non essential elements that are “suspected” to be harmful to humans.
The nonessential elements As, Cd, Hg, Pb have attracted most attention worldwide, due to their toxicity towards living organisms. Other elements (Al, B, Be, Bi, Co, Cr, Mn, Mo, Ni, Sb, Sn, Tl, V, W, Zn) are likely harmful, but may play some beneficial functions not yet well known, and should be more investigated.

Keywords (separated by “-”)	PHEs - Geomedicine - Human health - Toxicology - Carcinogenic elements

Chapter 11
Potentially Harmful Elements and Human Health

Claudio Bini and Mohammad Wahsha

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Keywords PHEs • Geomedicine • Human health • Toxicology • Carcinogenic elements

1 Introduction

Chemical elements of both geogenic and anthropogenic origin are usually present in large amounts in soils, sediments and waste materials which often contain elevated concentrations of potentially harmful elements (PHEs) such as As, Cd, Cr, Cu, Ni, Pb, Zn and others (Helios-Rybicka 1996; Lee et al. 2001; Navarro et al. 2008). Heavy metals, in particular, are considered to be among the most effective environmental contaminants, and their release into the environment is increasing since the last decades. Metals released in the environment may result from many different activities and sources and may enter into the environment by a wide range of processes and pathways (Hassanien and El Shahawy 2011). They can be transported, dispersed in the environment and accumulated in plants (Davies 1987; Alloway 1995, 2013), and then may pass, through the food chain, to human people as the final consumer, causing serious health problems as intoxication, neurological disturbances and also cancer (Bernard 1995, 2008; Steinnes 2009).

The metal-enriched areas, therefore, represent an ideal natural laboratory where to study the processes in order to provide descriptive models of the interactions between PHEs, the pedosphere, the biosphere and the hydrosphere. Environmental threats arise when a certain amount of potentially harmful elements (PHEs) is released in the surrounding areas and to waterways. Indeed, it is well known that PHEs may have toxic effects on living organisms (microbes, plants and animals, including humans). Depending on the nature of rocks and soils, a wide dispersion of these PHEs both in solution and in particulate form is possible (Sivri et al. 2010).

Atmospheric emissions are probably the most harmful to the environment, and consequently, to human health due to either the great quantity involved, or their widespread dispersion which may originate many different exposure pathways. In particular, three heavy metals (Hg, Pb and Cd) are of great concern to human health and to the environment, mostly due to their ability to travel long distances in the atmosphere before deposition (Hassanien and El Shahawy 2011).

It is generally recognized that environmental contamination with PHEs has increased dramatically since the dawn of the Industrial Revolution (Nriagu 1979), and the main receptor of contamination is soil. Soil is a complex system with several functions, not only ecological, but also social and economic, and fundamental to living organisms, including human population (Moreno-Jimenez et al. 2011). Yet, it is the primary source of several elements and substances that

humans intake with daily diet, and 98 % of food derives directly or indirectly from the soil (Coccioni 2011). Soil health, therefore, is of fundamental importance for human health, that is largely determined by mineral nutrition supplied by plants growing on soil: if a soil is contaminated, it is likely that also food crops are contaminated, posing potential concern to consumers.

The main soil and land contamination sources are both natural (rock weathering and soil genesis) and anthropic (industrial) processes, mining activities, agricultural practices, vehicular traffic, atmospheric fallout; all these are responsible for the disposal on land of potentially toxic substances such as sewage sludge, fertilisers and pesticides, persistent organic pollutants (POPs), polycyclic aromatic hydrocarbons (PAHs), polychlorobiphenils (PCBs) as well as heavy metals and other harmful chemicals.

Besides local pollution episodes, the most significant world soil pollution events in the recent history date back to the last century. A relevant amount of methyl mercury was released by a chemical factory in Japan over a long period (1932–1968), and entered the food chain determining acute poisoning by mercury to the local population, provoking severe neurological disturbance (Minamata disease). In the same years (1950), Cd-enriched wastewater from a mining plant was discharged on rice fields in Japan, determining chronic poisoning (itai-itai disease) with severe consequences in kidney functioning and bone deformation. A significant long-term contamination, lasting 15 years (1952–1966), occurred in the town of Hinkley (California, USA), where groundwater contaminated with Cr (VI)-rich wastewater from a chemical plant determined several cases of cancer to resident population. More recently (1976), an accident to the ICMESA chemical plant in Italy determined the release of dioxin in the atmosphere, and successive fallout to soils of a large area in Lombardy, with ca 250 persons affected by chlorine dermatitis. Moreover, dioxin is a known highly teratogenic substance responsible for severe foetal malformation, with still relevant effects after more than 30 years (Coccioni 2011). At Bhopal (India), in 1984, 40 tons of methyl isocyanate were discharged from a chemical plant producing pesticides, provoking 10,000 victims, and the mortality is still higher in that area than in other parts of India.

Besides possible lethal consequences to residential population, severe environmental accidents have occurred all over the world due to the discharge of chemicals on the land, in surface water or in the sea. Chromium-sludge discharged by leather tannery plants in the industrial district of Vicenza (Italy) has been shown to have contaminated hundred ha of agricultural land up to 10,000 mg kg^{-1} Cr (Bini et al. 2008). Petrol-chemical plants active at Porto Marghera (Venice, Italy) since the 1950s have been considered to be responsible for the contamination of the lagoon of Venice with several PHEs and organic chemicals (Bini 2008). The whole area has been classified as contaminated site of national interest, and a restoration project is ongoing. Heavy metals (As, Cd, Cr, Cu, Hg, Mn, Pb, Sb, Se, Zn) and organic compounds (PAH, PCB, Dioxin) have been identified as the main contaminants, owing to agrochemicals and industrial wastes discharged on soils and convoyed to the lagoon, provoking water and sediment contamination, decreasing biodiversity and shellfish disappearance (Bini 2008 and references therein).

In 1986, in the village of Schweizerhalle (Switzerland), 20 tons of herbicides and pesticides were discharged in the Rhine river, contaminating dramatically the whole area. In Italian territorial waters (Ionian sea), in 1974, the Yugoslavian cargo Cavtat carrying 900 drums containing more than 250 tonnes of Pb-tetramethyl and Pb-tetraethyl collided, and more than 20 tonnes were lost at a depth of 100 m below the sea surface (Tiravanti et al. 1980). Minor environmental effects were recorded 1 year afterwards.

Mining areas too are potential sources of severe environmental contamination (Bini 2012; this volume, Chap. 5), and resident population in the vicinity of mine sites is at high risk of suffering from serious diseases, with an elevated rate of enteric tumours (Zhao et al. 2012). Mine spoils are often disposed (or have been in the past), during active working periods, in the proximity of mine sites and conterminous land, provoking frequent accidents. In 1998, in Spain, 5 M cubic meters of highly contaminated sludge from a mining basin were convoyed to the Guadalquivir river to save the local natural reserve. In 2000, in Rumania, a fracture in a gold-mine dam determined outcome of more than 100,000 tons of mud containing cyanide. Fortunately, in both cases no victims were recorded. More recently, in 2010, the flotation basin of an aluminium plant ceased suddenly, provoking the outcome of 1 M cubic meters of highly alkaline red mud containing iron oxide and heavy metals in the Danube basin: it is estimated that this accident has been one of the biggest environmental disaster in the world, that will have important repercussions on human health for next decades (Coccioni 2011).

Perhaps the most known and impressive environmental disasters are those provoked by nuclear accidents like Chernobyl and Fukushima. In 1986, April, a reactor at the Chernobyl Nuclear power Plant in the former URSS (now Ukraine) exploded. The Chernobyl accident determined the emission in the atmosphere of about 85 PBq of radioactive materials, and the consequent fall-out of radioactive particles to vegetation and soils of several European countries. Radionuclides, in particular ^{137}Cs, were released at low altitude (<1,500 m), and their spatial distribution was strongly influenced by rainfall intensity and local topography. In NE Italy (nearly 2,000 km from Ukraine), because of radioactive particulate, forage for cattle was inhibited for some years, as well as fungi collection and cheese production in the contaminated areas (Giovani et al. 1991). The consequences of the accident on human health, particularly in Ukraine and Russia, were (and still are) very impressive: although the official report indicates only 65 persons dead, and possibly 4,000 affected by cancer and leukaemia, an estimate of presumable deaths related to the accident indicates tens thousands to millions of victims (Coccioni 2011).

At Fukushima, Japan, in 2011, March, a strong earthquake followed by a very anomalous ocean wave (tsunami) determined the breakdown of the Nuclear Power Plant, and the release of radiation in the atmosphere at a rate of 900PBq, with radiation levels exceeding the annual limits over a distance of 60 km. As of June, 2013, the exact chain of events was not known. The total amount of radiation released is also not known, and the likely number of deaths cannot be determined with the information available. Authorities spoke of two persons of the plant

personnel who died; however, one might expect around 1,000 extra cancer deaths related to the disaster.

Other nuclear fatalities occurred elsewhere in the world, and it was reported by newspapers that globally more than 300 patients receiving treatment for different cancer forms suffered radiation injuries, and at least eight died for over-exposition by ^{60}Co.

1.1 Soils and Human Health

The connection between soils and human health is still little recognized by general population. Also the medical profession, as pointed out so far by Voisin (1959), has largely ignored soils in their efforts to improve human health, but soil science should be the foundation of preventive medicine, as stated by Brevik (2013).

The idea that soils influence human health is not new, it has existed for thousands of years (Bible, Numbers, 13: 18–20), and received considerable attention in the twentieth Century (Brevik 2013). The scientific community started to pay attention to this concern since the 1960s (Webb 1964), and flourished in subsequent years, in combination with increasing epidemiological studies. Geochemical applications to epidemiology brought to develop the *landscape geochemistry*, i.e. the study of complex interactions within the system lithosphere-pedosphere-hydrosphere-biosphere, that is concerned with the mobility and distribution of elements in the environment. The relationships between environmental geochemistry and human health, including the incidence of disease patterns, have been investigated since the 1970s, particularly by Russian scientists (Kovalsky 1970). Afterwards, relevant contributions were given by several authors from different countries (Fortescue 1980; Lag 1980, 1984, 1987; Thornton 1993; Alloway 1995; Oliver 1997; Kabata-Pendias and Pendias 2001; Adriano 2001; Abrahams 2002; Deckers and Steinnes 2004; Van Oostdam et al. 2005; Kabata-Pendias and Mukherjee 2007), and ultimately by Alloway (2013), Brevik (2013) and Censi et al. (2013).

The early Russian approach (Perel'man 1966; Kovalsky 1970) included regional geochemical maps showing biogeochemical zones which reported the incidence of diseases as a result of geoepidemiological surveys at regional scale, and the first attempts to relate trace elements with diseases. Approximately in the same period, Thornton and Webb (1979) described the relationships between the level of Co in stream sediments and the incidence of pains in cattle and sheep. Parallel studies by Lag (1980, 1984) introduced the new concept of geomedicine as a multidisciplinary approach including geology, soil science, botany, zoology, microbiology, agriculture, animal husbandry, epidemiology and public health (Thornton 1993).

Born from the above (and others) contributions, the new scientific branch of the *medical geology* (termed *Geomedicine* by Prof. Lag), is based on the utilizing innovative approaches related to the most recent epidemiological, sanitary and geochemical knowledge. Medical geology is an emerging discipline, but since the Antiquity people discovered links between geology (in particular soil as the natural

substrate for food crops; Brevik 2013) and health, as reported by the early physician Paracelsus (1493–1541), who stated that *all substances are potential poisons, and the correct dose makes the difference between poison and medicine*.

A further evolution at worldwide level, initially referred to as medical geology, is now termed *health geography*, that is *"the application of geographical information, perspectives, and methods to the study of health, diseases, and health care of human population groups"*. It is grounded on the study of the relationships between environmental risk factors and adverse health effects, taking into consideration the worldwide distribution of illnesses, and the regional characteristics of pathological processes that generate geographically significant phenomena, thus allowing identification of areas where health hazard is higher.

Medical geology is now recognized as one of the exciting new areas of geological and pedological research, although at present this is not a formally established subfield of soil science. Nevertheless, as stated by Brevik (2013), increasing research in soils and human health is essential to protect the environment and to enhance general population health.

1.2 PHEs and Human Health

There is not a general agreement on the number and functions of chemical elements in the human body. According to Brevik (2013), there are 14 elements that are essential for plant growth, that come from the soil, and many of them are essential also for human health. Additional elements are needed by organisms. Eleven elements comprise 99.9 % of the atoms found in the human body: H, O, C, N, Na, K, Ca, Mg, P, S, Cl. Eighteen additional elements are considered essential in small amounts in the human diet: Li, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, W, Mo, Si, Se, F, I, As, Br, Sn, and most of them are supplied by plants.

Conversely, 22 chemical elements are considered by Coccioni (2011) essential to human health, owing to their physiological functions (Table 11.1). Only a part of them, however, are readily ingested with diet, absorbed and metabolized by the human body.

Some heavy metals, as copper (Cu), zinc (Zn) and iron (Fe), serve as micronutrients at low concentrations but they are toxic when in excess, while other heavy metals and metalloids, as lead (Pb), cadmium (Cd), mercury (Hg), inorganic arsenic (As), aluminum (Al) and nickel (Ni), are toxic even at very low concentrations, hence they are of particular health concern (Hassanien and El Shahawy 2011). Heavy metals have the ability to bioaccumulate in food chain, and children can be chronically exposed to them from different sources as air, water and food, leading to their accumulation in body tissues of children and causing various diseases, since they act as systemic toxins with specific neurotoxic, nephrotoxic, foetotoxic and teratogenic effects and can directly influence behaviour and impair mental and neurological functions via influencing neurotransmitter production and utilization (Obiria et al. 2010).

Table 11.1 Biological functions of selected essential elements t.1

Essential macroelements (×70 kg body weight)	Biological function	
Ca 1,000 g	Bone structure, neurotransduction	t.3
Mg 30 g	Bone structure, electrochemical regulation, enzymatic catalysis	t.4
Na 1.5 g	Electrochemical regulation, acid-base equilibrium, osmosis control	t.5
K 150 g	Electrochemical regulation, acid-base equilibrium, osmosis control	t.6
Cl	Electrochemical regulation, acid-base equilibrium, osmosis control	t.7
P 700 g	Bone structure, membrane structure, metabolic regulator	t.8
Essential microelements	Biological role	t.9
Fe	Oxygen and electron transport	t.10
Cu	Enzyme catalysis	t.11
Zn	Enzyme catalysis, protein structure	t.12
I	Metabolism regulator	t.13
Se	Enzyme catalysis, redox regulator, antioxidant,	t.14
Ni	Enzyme catalysis, redox regulator, antioxidant,	t.15

Adapted from Coccioni (2011) t.16

The primary sources of PHEs in the environment are geogenic and anthropogenic, the latter being the major cause of concern. Human health concern related to geological materials and processes, therefore, is more common than it was thought years ago: over three billions people have health problems connected to geological materials. Currently, there are few areas in the world not affected by metal pollution, as suggested by long-distance transported Pb in snow profiles in Greenland, which is approximately tenfolds that of Antarctic ice (Barbante et al. 2013).

Human health is vulnerable not only to individual sources, but also to the combined effects of various contamination sources. As stated by Nriagu and Pacyna (1988), nearly every industry discharges at least one metal into water or soil, with annual inputs of 82 t As, 22 t Cd, 954 t Cu, 25 t Ni, 796 t Pb and 1,372 t Zn, which are released to the environment from industry and other sources. However, it is important to remind that all the potentially toxic elements of concern to humans are present as natural background in small amounts in soil, water, food and air, as a consequence of rock weathering. Yet, it is well known the case of Cr and Ni in serpentine soils, and that of Cd and Mo in marine black shales. Thornton (1993) reports that excess Mo in soils from black shales causes Cu deficiency diseases such as ataxia in sheep and hypocuprosis in cattle. Conversely, a pedogeochemical survey in the Lake Nakuru national Park (Kenia), revealed low concentrations of Cu, Co, Se and P in volcanic soils, indicating Cu deficiency and the need of supplement for wildlife species in the Park (Thornton and Webb 1979).

Besides these natural geochemical anomalies, geochemical survey may also focus attention on anthropogenic anomalies (hot spots) related to chemicals

discharged on land by mining activities (Bini 2012; see this volume, Chap. 5), industry and urban sources (Bini et al. 2008; see this volume, Chap. 6). A famous example of a large environmental health investigation is that of an hotspot area with up to 500 ppm Cd around the village of Shipham (U.K.), one of the biggest Zn mine in EU (Thornton 1993).

A noteworthy concern is the finding of elevated Pb concentrations in the home environment, that may have significant implications on the health and mental development of children that habit the site, and are exposed to Pb-contaminated dust (Thornton 1993). The same apply to multi-element contaminated home gardens where vegetable is grown for kitchen: both gardeners and children playing in the garden are exposed to contaminated soils, and all the family may be affected by metal-contaminated vegetable consumption.

As a matter of fact, few causal relations have been shown until now between potentially harmful elements and human diseases. An exception to this statement includes the well known relationship between F content in water, human fluorosis and dental caries. Other exceptions are I concentration in food and endemic goitre, low Se intake, Keshan disease and Kaschin-Beck disease in China (Thornton 1993). All these aspects will be discussed in the next Sect. 2.

1.3 PHEs and Toxicology

The main effects of land contamination on human health are due to the contact with contaminated soils. Direct effects are brought about by ingestion, inhalation, and dermal absorption of soil components. Indirect links are through the atmosphere, hydrosphere and biosphere (see Abrahams 2002 for details).

From the toxicological point of view, ingestion of contaminated water, intake of toxicants by the food and inhalation of gaseous compounds are particularly relevant.

Toxic effects of PHEs to humans (Table 11.2) may occur with acute, subacute, subchronic and chronic symptoms. Chronic exposure to Cd may have effects such as lung cancer, prostatic proliferative lesions, bone fractures, kidney dysfunction and hypertension (Zhao et al. 2012). Chronic oral and inhalation exposure to As can lead to skin lesions and lung cancer, respectively. Exposure to Pb may cause plumbism, anaemia, gastrointestinal colic and central nervous system disturbance (Zukowska and Biziuk 2008). Hexavalent Cr is considered a human carcinogenic by both USEPA and IARC. Nickel can cause lung cancer, chronic bronchitis, emphysema and asthma.

One of the major concern to deepen is the essential element deficiency/excess; the imbalance may cause problems to crop production for human consumption, animal nutrition and ultimately to human health, as reported by Thornton (1993). Indeed, in some cases, toxic effects may occur in consequence of deficiency instead of excess of a given metal (Table 11.3). Several adverse health effects can arise from nutrient deficiencies; for example, the World Health Organisation (WHO

Table 11.2 Effect of PHEs on human health t.1

Element	Toxic effect	t.2
Arsenic	Liver cirrhosis, skin, liver and lungs cancer, Embryo theratogenesis	t.3
Beryllium	Lung cancer	t.4
Cadmium	Chronic kidney failure, bones deformation, loss of breathing capacity, high blood pressure, lung and prostate cancer, embryo theratogenic	t.5
Mercury	Neurological damage (*mercurialism*) asthenic-vegetative syndrome or Minamata disease. kidney damage, toxicity to the foetus and embryo theratogenic	t.6
Lead	Gastrointestinal damage, damage to both the neuro-muscular system and nervous system (*plumbism*), decreased fertility and sperm damage	t.7
Antimony	Respiratory system damage	t.8
Silver	Gastrointestinal, respiratory and liver damage,	t.9
Barium	Gastroentheritis, muscle paralysis, ventricular fibrillation and extrasystoles	t.10
Thallium	Neuronal damage, kidney and liver disease, foetus toxicity	t.11
Titanium	Irritation	t.12
Uranium	General biosystems and renal damage	t.13
Vanadium	Damage to the respiratory tract, skin and eyes, tremors, depression, kidney damage	t.14

Adapted from Coccioni (2011) t.15

2007) estimates about two billion people to be anaemic due to iron deficiency. Another soil-related form of malnutrition is iodine deficiency which leads to goitre, severe cognitive and neuromotor deficiencies and other neuropsycological disorders.

Selenium is now considered an essential microelement to animals, including humans. A low level of Se in diet can cause Keshan disease, a heart disease that likely has a viral component, and Kashin-Beck disease which results in chronic degenerative osteoarthrosis. Insufficient Se levels may also be associated with cancer, stunting of growth, immune system and reproductive problems, and multiple sclerosis (Schalin 1980; Roman et al 2014). Zinc-deficient soils are widespread and include about half the world's soils. Zinc deficiency may cause stunted growth, anorexia, skin lesions, diarrhoea, and impaired immune and cognitive functions.

Several elements normally required for human health may become toxic when present in high amounts (e.g. Co, Cr, Cu, Fe, Se, Zn, and others) (Abrahams 2002). Their effects on human health will be discussed in the next section.

Elements tend to have synergistic or antagonistic effects in the human body, so it is inadequate to discuss only single-element studies (e.g. Cd-Zn-Fe). Soil pH also influences nutrient and toxic element availability, with I and Se less available at acidic pH (Oliver 1997), and Fe, Al, Mn, Pb, Cd, Ni more available. Examples of antagonism include As against P and Sr against Ca, Zn against Ca, Fe, Cu, Ni (Oliver 1997).

Soils can also provide elements such as Pb, Cd, As, as well as radioactive elements (U, Cs, Ra, Rn), at levels that are detrimental to human health. Airborne dust can carry additional materials such as pathogens, harmful gases, organic chemicals, heavy metals, and radioactive materials that can cause other health problems. Airborne dust containing such toxins may carry these materials into the lungs, where they can enter the bloodstream.

t.1 **Table 11.3** Toxic effects on human health due to PHEs deficiency and excess

t.2 Element	Deficiency effects	Excess effects
Cobalt	Anaemia; weight loss; retarded growth rate	Possible inhibition of vitamin B12; goiter aggravation; cardiomyopathy; respiratory system irritation
t.3 Chromium	Alteration of glucose metabolism, with possible effects on the growth and metabolism of lipids and proteins	Kidney damage; respiratory system damage; chronic ulcers, perforation of the nasal septum
t.4 Iron	Anaemia	Vomiting; liver cirrhosis; defects in blood clotting; diabetes; arthritis; sexual malfunction; lung cancer
t.5 Magnesium	Kidney disorders; alcoholism; myocardial ischemia; conjunctivitis;	Decrease in blood pressure; respiratory paralysis; heavy fume fever
t.6 Manganese	Bone diseases, goiter aggravation	Epithelial cell necrosis and proliferation of mononuclear cells; neuropsychiatric disorders; liver cirrhosis; decrease in fertility
t.7 Molybdenum	Tachycardia, shortness of breath, headache, blindness, nausea, vomiting	Gout disease, toxicosis
t.8 Nickel		Cancer of the respiratory tract; dermatitis; headache; nausea, vomiting, cyanosis; gastrointestinal disturbances; weakness; edema; death
t.9 Copper	Anaemia, bone deformities	Abnormality of the nervous system, liver and kidneys; death
t.10 Selenium	Heart failure and various degrees of cardiomegaly osteoarthropathy	Weakness on hair and nails, skin lesions on sole, hands and neck; foetal toxicity
t.11 Zinc	Delay in growth and sexual maturation; dermatitis; susceptibility to infection and neuropsychological abnormalities in infants	Reductions in immune function and HDL cholesterol, fever
t.12		

t.13 Adapted from Fortescue (1980) and Coccioni (2011)

330 Heavy metals originate naturally from the weathering of rocks, but have also
331 been introduced to soils through human activities. They may occur as a by-product
332 of mining ores and are therefore present in mine spoils and in the immediate
333 surroundings of metal-processing plants. Electronic appliances such as computers
334 and mobile phones are also becoming a increasing source of heavy metals such as
335 Pb, Sb, Hg, Cd, Ni. Urban soils are particularly susceptible to significant accumu-
336 lations of potentially harmful elements. Fertilizers and agrochemicals are another
337 source of PHEs additions to soils and chicken feed (As) and swine feed (Cu, Zn).
338 The same PHEs, however, are likely found in sewage sludge, thus contributing
339 significantly to environmental pollution.
340 There are several elements, both essential and non-essential, that cause concern
341 from a human health perspective; these include, among others, Cu, Fe, Zn, Cr, Cd,
342 Hg, Pb. Human exposure to these metals can occur through different routes, such as
343 inhalation of dust. Metal transport occurs mainly through the atmosphere (see this

volume, Chap. 1), and influxes of African dust have been considered responsible for elevated levels of elements such as Hg, Se, Pb in European soils.

Other common pathways of exposure are consumption of contaminated crops and incidental or purposeful consumption of contaminated soil (geophagy) (Abrahams 2002).

Geophagy is the deliberate ingestion of soil, and offers several potential benefits to those who practice it, but there is the potential for serious health problems as well. The most frequently cited benefit is using the soil as a source of mineral nutrients. Medical uses of ingested soil material include the treatment of some types of poisoning and of gastrointestinal disorders (stomach aches, acid indigestion, nausea, diarrhoea (Abrahams 2002). Nevertheless, despite the potential advantages of geophagy, there are a number of negative effects due to soil ingestion: heavy metal toxicity, iodine deficiency disorders, soil parasitic infection.

Heavy metals are known to be bound to enzymes; metal bonding with enzymes may affect human health since enzymes cannot function normally. Damage to the central nervous system is common, leading to problems such as coordination, eyesight, the sense of touch, lowering intelligence quotient (IQ), bone deterioration, hypertension, increased cancer rates. Lead is the most problematic heavy metal due to the extensive variety of its sources.

Important radioactive elements sources are both natural (Rn from decay of uranium found in rocks) and anthropogenic (nuclear weapons manufactory and testing, accidental release from nuclear facilities such as Chernobyl (1986) and Fukushima (2011), burning of coal, smelting of non-ferrous metals, mining activities and medical waste). The most common health risks include various forms of cancer and genetic mutations. The level of risk and health problems are highly dependent on both the dose received and the amount of exposure time (see this volume, Chap. 10).

1.4 PHEs and Cancer

Some elements, such as mercury (Hg), cadmium (Cd), arsenic (As) and chromium (Cr), are toxic or carcinogenic even at low concentrations. Poisoning by exposure to PHEs is well known to affect central nervous system functions, damage blood composition, lungs, kidneys, liver and other vital organs. Long-term exposure can cause slower progressing physical, muscular, and neurological degenerative processes. Allergies may also occur and repeated long-term contact with some metals, or their compounds, may become carcinogenic.

Carcinogenic elements present common exposure pathways; the main way is inhalation, and the main target organs are those of the respiratory system (bronchus and lung), although other organs such as skin, stomach, prostate, kidney, urinary bladder, are reported as possible target organs (Apostoli and Catalani 2008).

Among the mechanisms which make plausible the carcinogenic action of metals, is reported their ability to generate reactive oxygen species (ROS) and other

intermedia able to induce direct damage to DNA by interacting with several enzymes and with cellular proliferation regulators. ROS act on cells with a direct effect on proteins, altering the activity and the conformation, or acting on redox-sensible proteins. The formation of metal-protein complexes, moreover, may interfere on cellular homeostasis, and determine conditions for an increase of cellular clones with mutagenic phenotypes.

Metals generally interact little and weakly with DNA; when it happens, interaction occurs mainly through two binding strategies: phosphate group of skeleton, and a variety of base electron-donors. Binding of metal with bases enhances spatial modifications which influence the interaction of specific enzymes with DNA (Franco et al. 2009).

Carcinogenic metals, therefore, are only a little mutagenic. As, Cd, and Ni inhibit DNA repair mechanisms, contributing to augment tumour inizialization induced by other agents, playing an important role in cellular proliferation, and favouring neoplasm development. Some metals, moreover, may induce codifying genes for cell-protective proteins such as metallothionein, and stress proteins (Apostoli and Catalani 2008).

The interaction of development factors on receptors through mutations or augmented expressions is among the mechanisms responsible for invasivity and metastatic characteristics of tumours. Other mechanisms responsible may be the communication block cell-to-cell, lipid peroxidation stimulation, flaming processes induction, endogenous DNA damage with possible chronic mutagenesis augmentation, increased intracellular radicals, interaction with detoxification mechanisms, redox reaction catalysis, DNA alchylation, cellular homeostasis alteration (Leonard and Bernard 1993).

It is generally accepted that the metal species (or the metal complex) influences in a determinant way the biological and toxicological activity of that metal. The effect induced by that element depends on its ability to enter the cell and to interact with target sites such as DNA. Crucial, therefore, are the chemical species, the oxidative state, charge, solubility, binding properties, stereochemistry, possibility to interact with other xenobiotics (Apostoli et al. 2006).

Since many elements present a more prominent oxidation state for carcinogenic activity (e.g. 2+ for Co and Ni; 3+ for Sb and As), it has been hypothesized that such metals utilize specific mechanisms that mediate their bioavailability as protein-carrier, transmembrane channels and formation of specific ligands. For example, bivalent metals may substitute for (or simulate) essential elements in many biological systems, enzymes and co-enzymes.

Oxyanions with V, Cr, As are chemical forms with high oxidation state, stable and able to cross cell membrane utilizing normal transport systems (phosphate or sulphate) and, once inside the cell, may act on specific enzymes. Besides common characteristics, however, every element is characterized by its own mechanisms, and by species and compounds more involved in carcinogenesis with respect to others.

The identification and classification of metal carcinogenicity by several associations and scientific societies results in different positions, particularly concerning

Table 11.4 International classification of selected carcinogenic elements

Elements	IARC[a]	ACGIH[b]	DFG[c]	EU[d]
Antimony	2B	A2	2	–
Arsenic	1	A1	1	R45
Beryllium	1	A1	1	R49
Cadmium	1	A2	1	R49, R45
Cobalt	2B	A3	2	R49
Chromium (VI)	1	A1, A2	2, 3B	R49
Nickel	2B	A1	1	R40, R49
Lead	2A	A3	2	R40
Vanadium	2B	A3	2	R68

Adapted from Apostoli and Catalani (2008)

[a]International Agency for Research on Cancer
[b]American Conference of Governmental Industrial Hygienists
[c]Deutsche Forschungsgemeinschaft
[d]European Union

the chemical species and compounds, as reported by Apostoli and Catalani (2008) (Table 11.4).

The International Agency for Research on Cancer (IARC 2006) attributed *certain carcinogenicity* with sufficient evidence for carcinogenicity for humans to compounds of Ni, As, Cr (VI), Cd, Be. *Suspected carcinogenicity* was attributed to metal Ni and alloys; instead, no carcinogenic effects were attributed to Cr (III), although a Cr (III) chronic phytotoxic effect was reported by Maleci et al. (2001). Inorganic Pb compounds are classified by IARC as *probable carcinogenic* for humans (class 2A), and soluble Co (II) salts, V and Sb compounds are suspected to have carcinogenic effects (class 2B).

Producing activities where exposure to PHEs is likely to occur are smelters (iron and steel founding with potential exposure to Ni, Cr, and several organic compounds such as PAH, phenols, amines), glass factories (exposure to As, Cd, Cr, Cu, Pb, Sb, Se, Zn,) (class 2A), steel welding and Ni-Cr alloys (class 2B); moreover, possible co-exposure to silica, asbestos, etc. are likely.

The Industrial Hygienists Association of the USA (ACGIH 2007) attribute to group A1 (substances known as carcinogenic to humans) inorganic insoluble compounds of Ni, As, Cr(VI), Be; furthermore, Pb-chromate, Ca-chromate, Sr-chromate, Cd compounds and Sb trioxide are included in group A2 (suspected carcinogenicity); Pb, Co, their inorganic compounds, and V oxide are included in group A3 (known carcinogenic for animals but with unknown relevance for humans). Inorganic soluble compounds of Ni and Cr(III) are included in group A4 (not carcinogenic for humans), elemental Ni in group A5 (unsuspected carcinogenic).

The German Association (DFG 2006) has included Ni and As, as well as their inorganic compounds, Pb-chromate and metals such as Cd and Be in group 1 (substances which cause cancer to humans, demonstrated by epidemiological studies and by evidence that the substance induces cancer through action mechanisms relevant to humans). Group 2 includes Cr(VI) inhalable compounds, Pb, V, Co,

as carcinogenic as results from long-time studies on animals (Apostoli and Catalani 2008). The same organization (DFG 2006) suggests exposure equivalents for carcinogenic substances for insoluble Ni compounds, and for Co, As and V compounds.

The European Union includes metals and related species in the list of carcinogenic and/or mutagenic substances according to the EC Directive 67/548/2006, and attributes cancer risk classes R49 (substances which can induce cancer by inhalation), R45 (substances which can induce cancer) and R40 (possibility to induce carcinogenic effects – insufficient proofs). In particular, Ni, Cr (VI), Cd, Be, Co and their compounds are assigned the R49, while As oxides, arsenates, Zn-chromate, Sr-chromate, Cd-chloride, Cd-fluoride are assigned the R45.

It is noteworthy to point out, however, that consistently with current legislation, carcinogenic substances are exclusively those chemical species and compounds that are assigned the cancer risk classes R45 and R49 proposed by EU (EC Directive 67/548/2006), and specifically substances, preparations, processes and works that expose workers to dust, fumes produced during metal refining at high temperature, or when the concentration of one (or more) substance (s) overcome the admitted limits for the classification of a chemical in carcinogenic categories 1 or 2 (IARC 2006).

The above recorded differences in the regulations are reflected also in environmental and biological indicators to be selected, and on the meaning of reference values, or biological limits, assigned to chemicals, as indicated in Table 11.5. For example, the environmental limit for a specific chemical species is frequently reported in comparison to the concentration value of the element such as it is, as well as a biological indicator of soluble compounds is utilized for monitoring exposure to the element such as it is.

The American Conference of Industrial Hygienists (ACGIH 2007) has set up biological limits for six elements (As, Co, Cr, Cd, Pb, V), and moreover established environmental threshold values for all the elements and related compounds. The German organization (DFG 2006) too has set up threshold values for the carcinogenic metals, with the exception of Be and Sb.

The Italian Society for Reference Values (SIVR 2005) has set up reference values for all the elements considered, specifying the different matrices by indication of the element as such, with the exception of As.

The Scientific Committee for Occupational Exposure Limits of the European Commission (SCOEL-EC 2008) has suggested occupational exposure levels (OELs) for the time weighted average (TWA), for short-term exposure limits (STELs), and biological limit values (BLVs). In particular, for those carcinogenic elements at exposure levels below which no carcinogenic effect is recorded, the OEL is not defined, but it is suggested that the lower is exposure, the less will be cancer development. Time weighted average(s) (TWAs) are expressed for Pb, Cr and their inorganic compounds.

The major problem, both theoretical and applicative, is posed by the speciation of the element of concern, which may influence environmental and biological measurements of exposure, risk assessment and sanitary/epidemiological

Table 11.5 Reference concentration values for selected elements t.1

Elements	ACGIH µg/l urine	DFG µg/l urine	EU – SIVR[a] µg/l urine	
Antimony	–	–	0.01–0.15	t.3
Arsenic	35	50–130	0.1–15	t.4
Beryllium	–	–	0.001–0.006	t.5
Cadmium	5.0	15	0.1–1.5	t.6
Cobalt	15	6–300	–	t.7
Chromium (VI)	10–25	12–40	0.05-0.30	t.8
Nickel	–	15–70	0.1–2.0	t.9
Lead	300	400	<0.5–3.5	t.10
Vanadium	50	35–140	0.1–1.0	t.11

The range is related to different metal compounds (Adapted from Apostoli and Catalani (2008)) t.12
[a]European Union and Società Italiana Valori di Riferimento

surveillance (Apostoli et al. 2006). Yet, fractionation of chemicals by selective extractions may enhance identification of the various compartments in which the element of concern is present, but chemical transformations and/or potential contamination may occur during analysis. Moreover, possible interferences among metals and other substances should be considered.

1.5 Concluding Remarks of Sect. 1

Differences in metal absorption, distribution, imbalance between toxicant effects and metal excretion can be explained, besides time exposure and prevention measures, from the physico-chemical characteristics of metals, as species, solubility, chemical reactivity. These could be utilized to interpret the different response of human organs towards carcinogenic metals, in terms of morbidity and/or mortality, as well as the high variability of epidemiological investigations on occupationally exposed workers, including clear evidence in some cases (e.g. roasting of Ni-bearing rocks), and little or no evidence in other cases, where the element of concern is determined at concentration levels even higher than background population values (e.g. Ni in serpentine soils and plants).

The need of information concerning chemical species and compounds actually classified as carcinogenic (or suspected) is recorded also in official documentation related to:

- registration of the total amounts of carcinogenic or mutagenic substances produced and utilized, or present as impurities or by-products in other substances;
- workers exposure (intensity and duration) measures;
- sanitary surveillance of workers showing somewhat health risk.

More accurate epidemiological investigations, combined with environmental and biological data which actually may qualify population exposure, and in

collaboration with other disciplines as metallurgy, industrial hygiene, analytical chemistry etc. could enhance comprehension of the effective risk posed by PHEs to human health.

2 Widely Recognized and Emerging Harmful Elements and Human Health

Potentially harmful elements (PHEs) in the environment may result from many different activities and sources and may enter into the environment by a wide range of processes and pathways. Generic sources of harmful elements include mining and industrial production such as foundries, smelters, oil refineries, petrochemical plants and chemical industry, untreated sewage sludge, dispersed sources such as metal piping, traffic and combustion by-production from coal burning power plants (Hassanien and El Shahawy 2011). Atmospheric emissions are probably the most harmful to the environment, and consequently, to human health due to either the great quantity involved, or their widespread dispersion which may originate many different exposure pathways.

Recent studies have focused on identifying the amount and distribution of some of the most common PHEs in the environment, and investigating the factors that cause contaminant exposure of human population. Some of these contaminants (e.g. Cd, Pb, Hg, As) are widely recognized as poisonous to human health (Filippelli et al. 2012); cadmium is known for kidney damage and bone pains which may lead to cancer; mercury for neurological disturbances; lead is known for its severe cognitive and behavioural disturbances; atmospheric dust may cause a variety of pulmonary diseases (Iskandar et al. 2012). Arsenic is a lethal poison, as represented also by the register Frank Capra in the famous fiction "Arsenic and old lace" (1944), and may provoke skin lesions and tumours, although at clinically achievable concentrations is used to induce apoptosis in malignant cells (Franco et al. 2009, and references therein). Conversely, elements known to be essential for health are the first row transition elements: Fe, Mn, Ni, Zn, Cu, V, Co and Cr, together with Mo, Sn, Se, I and F (Oliver 1997). Each has its specific role in the metabolism, and it cannot be wholly or partly replaced by any other element. Most of them act primarily as catalysts in enzyme systems (Oliver 1997 and references therein). Their roles range from weak ionic effects to highly specific associations with metalloenzymes; for example Cr acts as cofactor for insulin, and I makes the hormone thyroxine active. Chromium and selenium are essential to humans; their deficiency may induce illness, while excessive intake may induce cancer; Cr has been recognized as highly carcinogenic since the late nineteenth century (Adriano 2001), and Se proved lethal at intake up to 20 mg kg^{-1}.

There is no general agreement on the potential harm of certain elements, while some others are historically recognized as PHEs. In the next Sect. (2.1) most of the widely recognized PHEs (Cd, Pb, Hg, As, Cr, Se) will be discussed. Other

contaminants such as Al, B, Be, Bi, Co, Cu, F, I, Mn, Mo, Ni, Sb, Sn, Tl, V, W etc. are likely to affect negatively human health, but they are poorly studied at typical environmental concentrations, and little is known about their health effect at chronic exposure levels (Filippelli et al. 2012). Some of these "new" PHEs are referred to in Sect. 2.2 as Emerging Harmful Elements.

2.1 Widely Recognized Harmful Elements

2.1.1 Cadmium

Cadmium is typically a metal of twentieth century, even though large amounts of Cd have been emitted by non ferrous smelters during the nineteenth century (Bernard 2008). The trend in its end uses in the last two decades showed a steep increase (from 55 to 73 % of the total western world consumption) for batteries and a decrease in other applications. In the immediate future, it has been previewed by the World Health Organization (WHO 2003) that Ni-Cd battery market will grow continuously (e.g. power tools and telecommunication devices).

Cadmium does not have any physiological function within the human body (Godt et al. 2006), and is considered one of the most dangerous PTEs to human health, causing acute and chronic intoxications, even at very low exposure levels, on health and environment. It is not degradable in nature and once released to the environment, remains in circulation, being relatively water soluble, and tends to bioaccumulate (WHO 2003). It can persist in soils for decades; from soil, it is translocated to plants and the food chain, and ultimately accumulates in the body of people eating contaminated food. Cadmium is also present in tobacco smoke, further contributing to human exposure. By far, the most salient toxicological property of Cd is its exceptionally long half-life (estimate is 20 year) in the human body, particularly in kidneys and other vital organs such as liver and lungs (Bernard 2008).

The International Agency for Research on Cancer (IARC 2006) classifies Cd in Class 1 "*the agent is carcinogenic to humans*", and it has been identified as a priority hazardous substance under the EC Water Framework Directive (2006). Cadmium has been ranked at the sixth in the Top 20 list of toxic substances for significant human health hazard by US Poison and Disease Registry (Akynloye et al. 2006), and has been a focus of study on environmental pollution in the UN Environmental Programs (UNEP) and the International Commission on Occupational Health Organization (Han et al. 2009).

The acute toxicity, as first described by Friedrich Stromeyer (1817, cited in Godt 2006), can lead to kidney, bone, and pulmonary damages, while chronic effects have been recognized much later (1930–1940). Chronic exposure to Cd can have severe effects such as lung cancer, prostatic proliferative lesions, bone fractures, kidney dysfunction and hypertension (Zhao et al. 2012). Other effects are disturbance of Ca metabolism, *hypercalciuria* and formation of stones in the kidney.

Cadmium is a source of concern for industrial workers since the first investigations (1930–1940) on pulmonary, renal and bone lesions, and for population living in polluted areas (Bernard 2008). A survey on Polish workers of a lead-acid batteries plant, and exposed to Cd, showed significantly higher Cd levels in blood in comparison to general population (Wasowicz et al. 2001). Cadmium is absorbed by the body by inhalation (through the lungs) and by ingestion (through the digestive tract). This route of absorption plays an important role in case of bad hygienic habits such as not cleaned hands, ingestion of contaminated food, and smoking during occupational exposure.

An epidemic occurrence of bone pains, with patients showing a wide range of symptoms such as low grade of bone mineralization, high rate of fractures, increased rate of osteoporosis, developed in Japan since 1940s. The disease with the above symptoms (called *itai-itai*), was associated with Cd poisoning, and was related to consumption of rice grown on fields irrigated with highly Cd-polluted water (Godt et al. 2006). Further evidence was found by Honda et al. (2003). Similar findings were recorded in a study on 1,000 people from southern Sweden, with significant negative correlation between urinary Cd and low bone mineral density, particularly on persons aged more than 60s. Individuals included in this study were either battery plant workers, or inhabitants close to the battery plant. The exact mechanism of interference between Cd and bone mineralization remains to be discovered; it may be an indirect influence of renal dysfunction (Berglund et al. 2000).

After that early reports, a number of epidemiological studies were carried out worldwide in order to characterize Cd toxicity and assess exposure levels which could threaten human health. As a result, from the 1990s it has been suggested that Cd can generate adverse effects even from much lower exposure levels than was believed before. Kidney results the critical organ for which dose-response relationships are best documented (Bernard 2008).

The major pathway of exposure to Cd is both by ingestion and inhalation. Food ingestion is the primary exposure source for general population; the amount of Cd ingested daily with food in most countries ranges between 10 and 40 μg per day (WHO 2003; Bernard 2008). Cereals account for about 50 % of Cd intake. The WHO has established a provisional tolerable intake of 7 μg/kg body weight, i.e. 70 μg Cd for averaging 70 kg man, and 60 μg Cd for 60 kg woman, while the recommended intake for children is 2–25 pg day^{-1} (WHO 1996). However, even small concentrations in foods can have a significant effect in the long term because Cd accumulates in the body (Oliver 1997). The maximum permissible Cd value in blood for workers in Germany is 15, compared with the average blood Cd concentration in non smokers that is 0.5 μm/l (Godt et al. (2006).

Tobacco smoking is an important additional source of exposure for smokers. Since one cigarette contains approximately 1–2 μg Cd, smoking one pack per day results in a daily uptake of Cd that approximates that derived from food. As reported by Bernard (2008), absorption by the oral route varies around 5 % but can be raised to 15 % in subjects with low iron store. When exposure is by inhalation, between 10 and 50 % of Cd is absorbed, depending on the particle

size. With tobacco, an average of 10 % of Cd is absorbed. The absorption via lung is higher than gastrointestinal absorption (via the stomach): up to 50 % of the inhaled Cd may be absorbed. A major part of Cd in the human diet comes from agricultural products, the most important source being atmospheric deposition, followed by application of sewage sludge and waste products. Absorption through the skin, instead, is negligible.

The highest concentrations of Cd (10–100 mg kg^{-1}) are found in internal organs of mammals, mainly in the kidneys and liver, as well as in some species of fish, mussels and oysters. Accumulation in kidneys and liver is due to the ability of these tissues to synthesize metallothionein, a Cd-inducible protein that protects the cell by tightly binding the toxic Cd^{2+}ion (Bernard 2008). The protective effect of Zinc, an essential metal in human metabolism, towards Cd toxicity, determines the selective accumulation of Cd in the proximal tubular cells and thus in the renal cortex, where it increases during the person's life span. A possible perturbance of phosphorus and calcium metabolism may occur, with formation of kidney Ca-stones (Godt et al. 2006).

The major health hazard of Cd occurs when its concentration exceeds 200 pg Cd kg^{-1} BW, and the effects on health are greater in ageing people. *Proteinuria* (loss of low molecular weight proteins from the kidneys), *glucosuria* (loss of sugar) and *aminoaciduria* (loss of amino acids), and the excretion of Cd are early signs of Cd intoxication of the kidney (Oliver 1997). Diseases of the bone, (osteomalacia and osteoporosis) have been observed only in Japan where the effects of Cd toxicity were exacerbated by dietary deficiencies of Ca, vitamin D and protein. It seems that Cd affects Ca and vitamin D metabolism resulting in the decalcification of bones (WHO 1996).

Cadmium chronic poisoning causes two different kinds of health effects: damage of target organs, and non-specific changes for population as weakness, ease to suffering from illness, rise of morbidity and mortality (Han et al. 2009). Target organs are kidney, bones, prostate (urogenital system). Kidney damage is the main problem for patients chronically exposed to Cd; it is the first organ to display signs of toxicity, which probably represents the critical health effect both in general population and in occupational exposed workers. Cd nephropathy has been described in industrial workers exposed mainly by inhalation and in general population exposed via contaminated foods, with a total Cd concentration at 150–200 mg kg^{-1} in renal cortex (Bernard 2008).

Early indices of kidney damage are Cd concentrations in blood and urine; the earliest manifestation of Cd-induced renal damage consists in an increased urinary excretion. Indeed, Cd is mainly eliminated via the urine, but daily excretion is very low (0.005–0.01 % of the total body burden, which corresponds to a biological half-life of more than 20 year). As a severe secondary effect, the development of Cd-induced proteinuria is predictive of an increased mortality by heart failure, cerebral infarction, nephritis and nephrosis (Bernard 2008).

The disturbances of Ca and phosphate metabolism accompanying Cd nephropathy can cause bone demineralization through direct bone damage or indirectly as a result of renal dysfunction (Uchida et al. 2007; Agneta et al. 2006), formation of

kidney stones and bone fractures. Usually, bone damage has been considered a delayed sign of severe chronic Cd poisoning. Based on reports concerning the epidemic occurrence of Itai-Itai disease in China and Japan (1940–1950s, see above), a population-based study showed an association between skeletal damage and low-level environmental Cd exposure (Han et al. 2009). Conversely, higher Cd exposure by food (rice) ingestion determined consequent health effects such as renal injury, higher mortality, shorter survival time, and more unfavourable prognosis. Mortality of people by Itai-Itai caused by higher environmental Cd exposure has been reported to achieve 76 %, against 50 % of the control group (Han 2009).

Early indices for bone injury are bone mineral density, urine calcium, urine phosphorus; instead, association between urinary Cd and bone mass density has not yet proven. Skeletal damage (osteoporosis) too, accompanied with pain in the back, difficulties in walking, multiple bone fractures and renal dysfunction may be a critical effect of Cd exposure, but it is still unclear.

Other effects of Cd exposure are reported in literature, that concern various biological systems. Godt et al. (2006) report that the main pathway of Cd absorption is by inhalation, and Cd absorption through the human gastrointestinal tract is only 5 % of the ingested Cd amount (e.g. by food). Several factors can increase this amount, such as low intake of vitamin D, and Cd-counteracting nutrients such as calcium and trace elements as Zn and Cu. The respiratory system is affected severely by inhalation of Cd-contaminated air; Bernard (2008) points to the impairment of the pulmonary function suggestive of mild obstructive syndrome in workers exposed to relatively high concentrations of Cd by inhalation. Respiratory insufficiency and increased mortality rate from obstructive lung disease has been seen in workers with high exposure in the past (WHO 1992). One of the pathways of Cd absorption by a relevant portion of general population is inhalation of cigarette smoke. The human lung resorbes 40–60 % of Cd in tobacco smoke, in the form of Cd-cysteine complexes (Godt et al. 2006). Non-smokers show an average Cd blood concentration of 0.5 µg/l, while smokers generally have Cd blood levels 4–5 times those of non-smokers.

Adverse effects on the reproductive system biology due to Cd exposure are reported by several authors. Low dosage of Cd proved to stimulate ovarian progesterone biosynthesis, while high dosage inhibit it (Godt et al. 2006). Pregnant women exposed to environmental Cd might have an adverse effect in prenatal period (e.g. foetal growth retardation, premature birth, low birth weight, birth deformities, and an increase of spontaneous abortion) and a possible cause of male infertility (Falcon et al. 2002; Han et al. 2009). However, Cd does not cross easily the placental or the hemato-encephalic barriers, thus explaining its very low toxicity to the foetus and the central nervous system as compared with other heavy metals (e.g. Pb, Hg).

Further adverse effects are reported to be caused by Cd intoxication: intake of Cd-contaminated food causes acute gastrointestinal effects, such as vomiting and diarrhoea (Nordberg 2004). Mortality for heart failure, cerebral infarction and pancreatic dysfunctions too are reported as effects of Cd exposure among inhabitants living in a Cd-polluted area in Japan (Nishijo et al. 2006; Lei et al. 2007),

while Cd levels in blood, but not in urine, were associated in USA with a modest elevation in blood pressure levels (Bernard 2008).

Sarkar et al. (2013) report that Cd is toxic, nonessential and classified as a human carcinogen. Generally, it forces the expression of the stress proteins and depending on factors such as amount of exposure, time of exposure, the cell line and presence of other chemical species, the outcome could be apoptosis, growth inhibition, proliferation or carcinogenicity in animal cells. The mechanisms leading to cadmium carcinogenesis are primarily those involving oxidative attack by ROS, inhibition of DNA repair mechanisms and augmenting or diminishing the tendency to apoptosis (Sarkar et al. 2013).

There is proved evidence that Cd can cause several tumours. A prolonged exposure has proven to be carcinogenic to liver, kidney, lung, prostate, hematopoietic and other systems. Occupational exposure is linked to lung cancer and prostate cancer and severe testicular necrosis followed by high incidence of testicular tumours (Godt 2006), while links between Cd and cancer in liver, kidney and stomach are considered equivocal (Waalkes 2000). Cadmium plays a recognized role in the aetiology of prostate cancer in battery plant workers. Vinceti et al. (2007) observed a dose-response relationship between Cd exposure and prostate cancer risk. The association between Cd exposure and risk was also confirmed by a multivariate analysis including body mass index, smoking, family history of prostate cancer, protein and lipid consumption. The biological plausibility of a Cd-prostate cancer relation in humans is also supported by the results of several experimental studies, which suggested the possible existence of a threshold above which Cd exposure becomes of concern (Vinceti et al. 2007).

Early investigations (Kolonel 1976) suggested an association of Cd and renal cancer in humans, recently confirmed (Il'yasova 2005). Consequently, the IARC decided to classify Cd as a human carcinogen group I, *mainly due to Cd assumption by respiratory system pathway*. Depending on factors such as amount of exposure, time of exposure, the cell line and presence of other chemical species, the outcome of Cd exposure could be growth inhibition, proliferation or carcinogenicity in animal cells, and apoptosis (Franco et al. 2009; Sarkar et al. 2013).

The mechanisms leading to cadmium carcinogenesis are primarily those involving oxidative stress, inhibition of DNA repair mechanisms and augmenting or diminishing the tendency to apoptosis. The majority of Cd is transported in the circulatory system bound to proteins such as albumin and metallothionein. The first organ reached after uptake into the gastro-intestinal-blood is the liver. Here Cd induces the production of metallothionein. After consecutive hepatocyte necrosis and apoptosis, Cd-metallothionein complexes are washed into sinusoidal blood; part of absorbed Cd enters the entero-hepatical cycle via secretion into the biliary tract (Godt et al. 2006). However, the mechanism of Cd carcinogenesis remains largely unknown (Bernard 2008).

Diagnosis of chronic Cd poisoning basically relies on the screening of proximal tubular renal dysfunction and the assessment of the cumulative exposure to Cd using environmental or biological indicators. Biomarkers offer the possibility not only of evaluating the human exposure to environmental pollutants, but also to

study the potentially harmful effects for the health associated with such exposure. For example, Begona Zubero et al. (2010) found increased levels of urine Cd in population living close to an incinerator plant, with levels similar to those carried out in Europe and USA. Studies on industrial workers in the 1980s have derived a threshold of urinary Cd of 10 μg/g creatinine for the development of tubular proteinuria. This threshold serves now the basis for occupational exposure limit of 5 μg/g creatinine currently in application in most industrialized countries (Bernard 2008). However, studies in Belgium and Sweden have concluded that tubular dysfunction is likely to occur in the general population from thresholds of urinary Cd in the range of 1–2 μg/g creatinine.

There are no efficient treatments for chronic Cd poisoning. Even after cessation of exposure, renal dysfunction and pulmonary impairment may progress. The only possible intervention is removal from exposure, and primary prevention is needed in order to maintain low levels of Cd in the environment or in the food chain.

2.1.2 Lead

Lead has been probably one of the first pollutants to receive widespread attention as a causative agent for health-related effects (Apostoli et al. 2002; Bierkens et al. 2011). It has been used for centuries since the Roman age, and has been known as toxic since the second century BC in ancient Greece (Oliver 1997).

Over decades, lead has been used in many different applications: building materials, pigments for glazing ceramics, batteries and pipes for transporting water (Hassanien and El Shahawy 2011); in the last century, in particular, it was largely used as additive in fuel for engine, posing important health concerns. Yet, lead poisoning is currently one of the most prevalent public health problems in many parts of the world (Nriagu 1988), especially considering the intake of concentrations regarded as nontoxic over long periods (Davies and Wixson 1987).

Numerous cases of lead poisoning have been reported since the 1980s. On February, 21, 1988, local newspapers in U.S.A. reported that it was a miracle that Mr and Mrs Wallace survived to lead intoxication induced by kitchen artistic pottery. This case poses the problem of the release of toxic elements, often necessary for manufacturing of fine articles (pottery, food containers, etc.). Refined Pb-glasses ("crystal glasses") are effective metal-retaining objects, and information on metal release is not current. Conversely, ceramic pots with high Pb content are well known for releasing fluorine if not oven-dried at the correct temperature.

As a consequence of large utilization, lead is a widespread contaminant of the soil, generally arising from pollution from mineral exploitation and industrial wastes, and from atmospheric deposition (Oliver 1997). The high occupational exposure-related hazard occurs in the processes of lead ore smelting, welding and cutting of metal constructions, lead-containing paints, casting of non-ferrous metals, production of batteries etc. The main pathways for Pb exposure, that may affect both general population and exposed workers, are via inhalation of atmospheric particles, and ingestion of contaminated food. Actual levels of lead found in

air, food, water and soil/dust vary widely throughout the world and depend upon the degree of industrial development, urbanization and lifestyle factors (WHO 1985). In general, lead-contaminated house dust and soil is the major source for blood lead levels in children (Lanphear et al. 2002). Lead levels in dust depend on factors such as the age and condition of housing, the use of lead-based paints, lead in petrol and urban density (Bierkens et al. 2011).

Lead is currently classified as number 2 in ATSDR's (Agency for Toxic Substances and Disease Registry) Top 20 list (ATSDR 2007).

The WHO (1996) reported that dietary intakes of Pb range on average between 20 and 282 pg day^{-1} for adults, and between 9 and 278 pg day^{-1} for children, who can take up more if there is too little Fe in their diet (WHO 1996; Oliver 1997). A large intake is regarded as 2,500 pg day^{-1}. A concentration of 250–550 pg Pb L^{-1} in the blood of children indicates poisoning (WHO 1996).

Because of the established link between exposure to lead and cognitive development, children are considered an important and vulnerable target population (Bierkens et al. 2011). Indeed, the nervous system of small children is especially sensitive to Pb, because of the incomplete development of the barrier between blood and brain, and the children can become retarded (Oliver 1997).

Pocock et al. (1994) related Pb blood concentrations of 100–200 pgL^{-1} with intelligence (IQ) in children over 5 years of age. The results of the study showed an inverse association between IQ and Pb concentration. Lead also causes metabolic disorders and neurophysical deficits in children, and affects the haematopoietic and renal systems (Hutton 1987). Lead interferes with the incorporation of iron into the protoporphyrin leading to anaemia, and causes renal damage (WHO 1996). Lead has been also the first metal to be linked with failures in reproduction (Peereboom-Stegeman 1987): it can cross the placenta easily. Moreover, Pb is transferred from the mother to the foetus, and young children show a higher exposure pattern per unit body weight due to their higher contact with soil and dust, and higher intake rates. It also affects the brain, causing hyperactivity and deficiency in the fine motor functions (Oliver 1997).

Occupational Pb exposure may result in chronic poisoning. It mostly affects the hematopoietic and nervous systems, and may cause plumbism, anaemia, nephropathy, gastrointestinal colic, and above all damage of the central nervous system (Zukowska and Biziuk 2008; Zhao et al. 2012; Hassanien and El Shahawy 2011).

The neurotoxicity of Pb is more critical for the developing foetus and the growing children. Pruvot et al. (2006) report that infantile lead poisoning in the vicinity of the main European smelter showed 10–15 % of children from 2 to 3 years having a Pb-blood level higher than 100 μm PbL^{-1} of blood, owing to strong lead contamination by indoor and outdoor dust of the schools and houses of these children. The ingestion of vegetables produced in kitchen gardens in the contaminated area, and the ingestion or inhalation of contaminated soil particles, proved the main key routes of exposure to lead, in particular via hand-to-mouth transfer. In addition, many studies (e.g. Dudka et al. 1996; Douay et al. 2005) have described the metal transfer to crops grown on soils contaminated by atmospheric deposits, and values recorded in the produce often exceed the European reference

values (EU Directive March, 8, 2001) thought to cause a medical risk (Hough et al. 2004). The highest metal concentrations were measured in wheat and barley grains (range 0.02–14.42 mgPbkg^{-1}) and to a lesser extent in maize (Pruvot et al. 2006). Previous epidemiological studies carried out in the investigated area (Leroyer et al. 2000) showed that metals present in the various compartments of the environment contributed in a substantial way to the exposure of local population. In particular, lead accumulates mainly in bones (95 %) and teeth in the form of chelates, as reported by Martinez-Garcia et al. (2005), who examined bones of inhabitants in territories where mining activity took place so far, and are in contact with processed metals.

Another human health effect due to lead exposure is reported by Giaccio et al. (2012). A comparison of data on heavy metal pollution with data related to the semen quality in the town of Neaples (Italy), the core of the Vesuvian volcanic district, showed a consistent evidence for an association between Pb (and also Sb) concentration in soils and reduced semen quality. The density distribution of subjects with male infertility problems is higher in areas where the concentration of Pb and Sb (traffic related elements) is greater. People living in unpolluted areas are exposed at lower infertility risk while those who live in polluted metropolitan areas are exposed to higher infertility risk.

Lead (Pb) is probably the most intensively biomonitored chemical with continued concern about its potential health impact (Smolders and Schoeters 2007). Pb is an ubiquitous environmental pollutant with a long history in human biomonitoring (HBM) programs (Bierkens et al. 2011).

Although lead has been monitored extensively in the European population, a consistent biomonitoring dataset is not yet available. Data diverge with regard to regional scale, gender, age groups and sample size. Especially for women of childbearing age and young children more data are required as they are the most susceptible to the impact of Pb on the developing brain.

There are only few reports concerning human antioxidant barriers under occupational exposure to lead. Wasowicz et al. (2001) report that occupational Pb exposure may result in chronic Pb poisoning (up to 500 μg Pb L^{-1}), with cell damage. An increase in lipid peroxidation (measured as thiobarbituric acid reactive substances-TBARS) has been recorded in blood of exposed workers, together with a decrease in essential Zn concentration, compared with the reference group.

It is also important to recall that knowledge acquired from experienced cases of workers affected by diseases related to inappropriate protection to metal exposition needs decades to perform adequate legislation acts aimed at improving the quality of life. Yet, it is unlike that old professional diseases as plumbism, but also asbestosis, silicosis, fluorosis, mercurialism nowadays could be ascribed to new agents. The demonstration of effects of lead, (e.g. reduced learning capacity particularly on children, damage to reproductive apparatus), besides the brain damage (Chem. Eng. News, 1982, August, 9), was largely far from determining a reduction/disappearance of the Pb-tetraethyl from fuel for engine, as it was achieved years after. Indeed, during the last century, the lead content in fuels was a main source of pollution to the environment and, particularly, the lead released to

the atmosphere was especially hazardous to children. Today most of the 25 millions of tons of lead produced every year is used in batteries. Exposure assessment to emissions of lead implies to identify and quantify the sources, how it can be dispersed in the environment and which adverse effects it might cause on human health and on the ecosystem.

2.1.3 Mercury

Mercury, as well as lead, is considered non-carcinogenic; instead, it is a known neurotoxic. Industrial utilization of mercury (chemicals, electronics, pharmaceuticals, agro-zootechnicals) is of particular environmental concern. Although it is present in the industrial emissions in the elemental form Hg, it forms easily organic and inorganic compounds. Dimethyl-Hg is highly volatile, and may disseminate contamination in areas not immediately proximal to the pollution source. Methil-Hg, instead, is stable in aquatic environment, and passes easily to the food chain following the sequence phytoplankton – zooplankton – predator fish – humans, having the ability to concentrate up to 10,000 times.

Mercury in the metallic state is less toxic than organic and inorganic compounds, being scarcely reactive with living substances. Hg-vapours, instead, are highly harmful, being promptly absorbed by the respiratory apparatus, generating systemic toxicity. Their maximum tolerable concentration is 0.050 mgm^{-3}air. The ordinary pathways of Hg-compounds exposure are oral and inhalation; organic compounds are more toxic than inorganic ones (e.g. the toxic dose of methyl-Hg for cattle is 13 mg kg^{-1}, while that of HgCl is 10 g), and are known to have provoked severe poisoning episodes in Iraq in 1972. The historically most known poisoning episode by methylmercury was that occurred at Minamata, Japan, in 1953. A local chemical plant, that utilized inorganic mercury as a catalyst, discharged waste material in the marine bay in front of this small village. Aquatic microorganisms transformed inorganic Hg into methylmercury, that was absorbed promptly by algae and phytoplankton, and afterwards concentrated in fish that feed plankton. Local inhabitants, who fundamentally eat local contaminated fish, were the first to present poisoning symptoms. The final balance was actually dramatic: 121 toxicant people (46 with lethal consequences), and a series of severe effects on infants of pregnant women at the moment of the accident.

Mercury compounds are protoplasma general poisons that bock the enzymatic activity, provoking protein precipitation and acting as direct corrosives. Endocellular metabolic ways are interrupted by enzyme inactivation operated by mercury. Mercury entered in the circulatory system is promptly oxidized to Hg^{2+}; this may bind the plasma and tissue proteins. A portion of Hg crosses the blood-brain barrier, enters the brain and there undergoes oxidation and reacts with functional groups-SH of proteins, accumulating in the brain tissue. The highest Hg concentration is generally found in kidney; the metal is excreted by the urinary system or by the faecal material.

Prolonged inhalation of Hg vapours may provoke respiratory system irritation and pulmonary inflammation, and acute edema, with insufficient respiratory activity and lethal evolution within 24 h. Acute poisoning by inorganic-Hg is characterized by stomatitis, oral cave and stomach pains, vomit, diarrhoea, anuria, shock conditions and finally death. Chronic intoxication evolves generally in a more sneaky way, with symptoms such as tremors, frequent diarrhoea, reduction of visual capacity. Gastro-enteric disturbances, acute nephrites, bronchitis, pulmonary edema, haemorrhagic episodes, liver necrosis, tubular renal necrosis also are likely to occur.

Toxicological effects of mercury compounds on both plant and animal life have long been recognised, but it was not until the above quoted disaster at Minimata Bay that the subject received worldwide attention (Rahman et al. 2000).

Exposure of mercury to the general population is mainly through the diet and dental amalgam. In foodstuffs, mercury is usually in the inorganic forms and of very low concentration. The exceptions are fish and fish products, which are the main sources of methylmercury in the diet.

The mercury content in hair is a useful indicator of exposure to methylmercury via fish intake in non-occupationally exposed people. When evaluating exposure to low concentrations of inorganic mercury, interference from methylmercury exposure can dominate blood analysis; therefore, an alternative biological matrix such as hair or urine is preferred.

2.1.4 Arsenic

Arsenic is present in nature as sulphides (As_2S_2 and As_2S_3, $FeAs_2S$), and as impurity in carbon, and is recovered as As_2O_3 from the fusion of mixed sulphide (Cu, Pb, Zn) minerals. Agrochemicals containing As have been widely used in the past, leaving diffused environmental contamination.

Arsenic is a toxic metal, especially in the state of AsIII. High contents of As naturally occurring in groundwater have caused severe problems in some regions. The most well known case is in the Bengal delta (Bangladesh and part of India), where over 40 M people were estimated to be at risk from As in drinking water (Steinnes 2009). Besides its toxicity, arsenic is well known also as a carcinogenic element that is widespread in the environment. Arsenic pollution has been reported worldwide, and some areas in South-East Asia and South America are particularly polluted (Liu et al. 2011).

Toxic effects of As compounds (e.g. oxide, arsenite, arsenate) are known since long time. Their toxicity is inversely proportional to the elimination velocity from the body, and increases in the following order: organic compounds $<$ arsenate $<$ arsenite $<$ arsine. Given the variable species-specific sensitivity and the multiple factors that influence its toxicity, it is difficult to assess the As toxic dose in animals; in many species, the lethal dose is in the range 1–25 mg kg^{-1} arsenite, while As_2O_3 is tenfold tolerated (Beretta 1984).

The As penetration pathways in the organism are oral, pulmonary and skin absorption. Ingestion is the main pathway of exposure to As, and arsenite is the best absorbed, while arsenate is slowly absorbed in the gastro-intestinal tract and is mostly eliminated by faeces. A prolonged ingestion proved a significant incidence of skin tumours as well as other cancer forms to lung and liver. Foetal malformations, moreover, have been recorded in pregnant subjects having assumed As (Shu 1973).

Acute poisoning by inorganic-As is responsible for elevated, and rapid, mortality. Death is preceded by colic pains, tremors, vomit, diarrhoea, prostration, collapse within 1–2 days.

Chronic poisoning is less frequent, and symptoms are skin lesions, damage to renal and gastro-intestinal apparatus, diarrhoea, intestinal mucous inflammation.

Human exposure to inorganic arsenic occurs via inhalation of industrial dust and ingestion of contaminated drinking water and food. Estimates of dietary intake range from 7 to 330 mg day^{-1}. Approximately 80–100 % of the inhaled and ingested arsenic is absorbed through the gastrointestinal tract and lungs but up to 50–70 % of the absorbed arsenic is eliminated mainly through urine and to a lesser extent through hair, nails and faeces.

In high doses arsenic is toxic, with the toxicity depending on the oxidation state. Toxicity decreases in the following order: arsine, inorganic As(III), organic As(III), inorganic As(V), organic As(V), arsonium compounds and elemental arsenic (Rahman et al. 2000).

Arsenic toxicity occurs if 3 mg day^{-1} are consumed for 2–3 weeks (Oliver 1997). Phillip et al. (1983) found evidence of a clustering of malignant melanomas where As concentration exceeds 30 g As kg^{-1}soil. They also reported that children, of 3 months to 36 months of age, are vulnerable to the effects of As. Thornton (1996) suggested that As in South-west England might account for the high incidence of malignant melanoma there.

There are elevated concentrations of As in drinking water in several countries in South-East Asia, and these are thought to cause skin disorders, *hyperkeratosis* (increased thickness of the upper layer of skin) of the palms of the hands and the soles of the feet together with *hyperpigmentation* (increased melanin), vascular disorders (e.g. Blackfoot disease, a form of gangrene), rashes (Tseng 1977; Thornton 1996), and cancer of the internal organs (Chen et al. 1992). When As is inhaled it increases the incidence of lung cancer, but when ingested it causes skin, lung, bladder, kidney and liver cancers. Steinnes (2009) reports that children exposed had a significantly lower body mass index, more underweight, more stunted.

Normal hair contains small quantities of As, ranging from 50 to 400 mg g^{-1}, but the level is greatly increased during excessive intake of arsenic. According to Rahman et al. (2000), the profound accumulation of arsenic in hair during exposure is of value in the diagnosis of arsenic poisoning.

Some authors have claimed that arsenic levels in human hair from healthy individuals should be <1 μg/g (Liu et al. 2011). However, others have suggested that the background concentration for human hair arsenic is <3 μg/g. Consistently, the mean arsenic concentration reported by Liu et al. (2011) in hair samples from

children living in Pian de' Gangani (Montalto di Castro, Latium, Italy) was 0.159 μg/g and the median was 0.152 μg/g. Man et al. (2002, in LIU et al 2011) reported an arsenic concentration of 0.17 ± 0.14 μg/g in hair samples from children aged 6–15 years. The arsenic concentration in hair from blackfoot disease patients (0.56 ± 0.41 μg/g) in Taiwan, China was significantly higher than that in hair from healthy people (0.56 ± 0.41 μg/g) (Liu et al. 2011). The arsenic content in human hair samples from individuals in arsenic-affected areas of West Bengal, India ranged 0.17–14.39 μg/g, with a mean of 3.43 μg/g and median of 2.29 μg/g. The mean hair arsenic concentration for a patient group drinking contaminated water in Bangladesh was 14.1 μg/g, while in a group drinking uncontaminated water it was below 3.0 μg/g.

Human hair arsenic concentrations in children are typically higher than in other age groups. This may be caused by different rates of arsenic metabolism resulting in differing accumulation of arsenic. However, the levels of arsenic in human hair are likely variable because individuals live in areas with different background arsenic concentrations. For example, in Italy, in the Venice region, As concentration in soils exceeds the regulatory guidelines up to 50 mg As kg^{-1} soil, as reported by Ungaro et al. (2008), in comparison to conterminous regions that exhibit As levels below the guidelines.

Arsenic accumulation in the human body is related to the strength of the metabolism. Younger adults accumulate less arsenic than other age groups due to their robust metabolism. Children and the elderly have relatively weak metabolisms, and they may accumulate more arsenic than other age groups when exposed to the same levels.

Other illness and disturbances due to As exposure are reported in current literature. Arsenic poisoning is known to produce polyneuritis in children who burned coal with a high As content. Arsenic (and Mn) have also been suggested as ototoxins affecting hearing (Chuang et al. 2007).

2.1.5 Selenium

Few chemical elements have risen research interest in the last decades as Se, that is known since long time for its toxicity to mammals (Gennaro Soffietti and Nebbia 1984); only since some decades, instead, its role as microelement in physiological and pharmacological processes has been focused, and recent research allowed to identify numerous pathologic forms derived from its deficiency (Roman et al. 2014). Indeed, selenium is now recognized as an essential nutrient for animals: Se-containing enzymes and proteins are essential for normal growth, development and metabolism in animals. Se concentrations in soils, pastures and animal blood correlate closely with each other, and with areas where Se-responsive disorders have been found.

Se is also known to be an antagonist to other heavy metals such as Cd, Hg, Pb, and also to have an antioxidative effect on lead-induced oxidative stress, and on oxidative damage in human sperm cell DNA (Chuang et al. 2007).

The geographic distribution of Se is not uniform. Some areas in the world (e.g. part of USA, Colombia, Great Britain) are characterized by large amounts of Se (up to 1,000 mg kg^{-1}) in soils, and vegetation may uptake Se amounts that may pose toxicity problems to living organisms, humans included. Other countries (e.g. Oceania, part of USA and most European countries, including Italy), instead, are characterized by low levels (less than the optimal concentration to avoid deficiency effects: 0.1 mg kg^{-1}) of Se in soils and vegetation (Cottenie 1979). It has been recognized as an essential trace element for humans and animals based on its presence in antioxidant systems and in hormone balance. The major use of Se is in the electronic industry (semiconductors, photovoltaic, solar cells, medical imaging equipments, glass industry). Natural food sources high in Se are cereals (corn, wheat, and rice), nuts, legumes, animal products (beef, chicken, eggs, cheese) (Gbadebo et al 2010). Anthropogenic Se pollution, derived by industrial activities (electronics, photovoltaic, glass, ceramics, paints, rubber, steel, plastics), is limited to the most important urban agglomerates, and does not pose serious environmental problems.

Selenium has a nearly paradoxical behaviour, since a concentration of 0.1 mg kg^{-1}Se in diet is considered essential for mammals, while a concentration of 0.4 mg kg^{-1} presents a noteworthy toxicity. Generally speaking, Se toxicity varies depending on the chemical species, with the organic ones that are more toxic than the inorganic. Moreover, Se toxicity is influenced by interrelations and counteracts with other chemicals (e.g. As, Cu, Hg, Cd), by formation of Hg-Se and Cd-Se complexes that are relatively harmless.

Low Se concentration in soils may lead to low Se uptake, low Se in the food chain, and low Se intake, provoking increasing risk of cardiovascular disease, coronary heart disease and cancer in humans.

The relation between the effects of Se deficiency and toxicity in the soil and health are most clear in some areas in China, where the Se concentration in crops is variable. The first disease associated with Se deficiency was Kashin- Beck disease, an endemic osteoarthropathy (Oliver 1997). It results in chronicle arthritis and deformity of the affected joints in children and teenagers. Muscular weakness is also a characteristic (Steinnes 2009).

Another typical disease associated with Se deficiency in China is Keshan disease, a cardiomyopathy found in young women and children. The symptoms are myocardial necroses, and weakness of the heart muscle (Oliver 1997). Low selenium levels have also been found in many disease states, including various forms of cancer, acute myocardial infarction, severe rheumatoid arthritis, cirrhosis of the liver and conditions exhibiting a compromised health status (Rahman et al. 2000). In addition, deficiency of Se is implicated in the weakening of the immune system, with muscular degeneration, impeded growth, anaemia, liver disease, and with endemic neuropathy and urinary tract tumours (Oliver 1997). Other symptoms of Se deficiency include muscle pain, weakness, and loss of pigments in hair and skin, and whitening of nails beds (Gbadebo et al. 2010).

The disease is likely associated with vitamin E deficiency (WHO 1996): Se deficiency impairs the antioxidant defences of the body, but Se combined with

vitamin E act synergistically as antioxidants to restrict tissue damage from oxidative reactions, and in part explain the role of Se deficiency in the pathogenesis of atherosclerosis and multiple sclerosis (MS).

Schalin (1980) observed a clear correlation with the geographical latitude of developed areas, Se deficiency and high prevalence of multiple sclerosis, and suggested the operation of an infective agent. However, it remains unlikely that MS is a disease of predominantly genetic origin since the world distribution suggests the opposite. Another strong argument supporting the hypothetical role of Se in MS is the fact that the only disease with a similar worldwide distribution is cancer of the colon, a disease convincingly related to lack of Se.

The selenium intake is generally through dietary sources, and is frequently below the safe range of 50–200 μg/day recommended daily intake of Se by the US national research Council. Health benefits of Se are partly explained by its antioxidant effect. It may delay or prevent the onset of cancer and also have anti-aging effect. If consumed in overdose, it may have toxic effects (Gbadebo et al. 2010).

Selenium toxicity in humans and animals is a much rarer problem than Se deficiency, but it occurs at sites where high soil Se concentration is combined with high uptake by plants (Alloway 2013).

Symptoms of Se toxicity are fatigue, hair loss, white blotchy nails. Se was found to be an environmental toxin responsible for health problems in livestock grazing on soils with high Se content. Dietary supplementation of 200 μg Se per day significantly reduced lung, prostate and colorectal cancer in humans. Chronic Se toxicity is caused by intakes of 2–4 mg/day or prolonged intakes of 1 mg/day. Chronic symptoms of excessive Se include morphological changes in fingernails, nail brittleness and loss of hair as well as nausea, vomiting and skin lesions.

Selenium is rapidly absorbed by the gastro-intestinal tract, and binds to plasmatic proteins, with albumins and globulins as carriers (Mc Murray and Davidson 1979). Administration of toxic amounts leads to Se accumulation in various organs, with the following order: kidney > liver > lung > heart > muscles > brain. Current knowledge on the metabolic reactions within living organisms is rather fragmentary and not reliable to an organic framework. Many Se compounds follow the same metabolic ways than S compounds, the two elements being isomorphic; for example, a possible metabolic scheme for selenite is the following: Selenite ($Se0_3^-$) reacts with glutathione (GSH) forming derivates such as selenodiglutathione (GS-Se-SG); this is metabolized to form selenidric acid (H_2Se), which is methylated and volatizes, contributing to decreasing Se concentration in organisms (Venugopal and Luckey 1978). A minor pathway of Se elimination is via urinary and faecal systems.

The toxic effects of Se can, at least in part, be explained by formation of Se derivatives of glutathione that function as redox-cycling agents generating reactive oxygen species (ROS). The net effect of Se at excessive levels is therefore not as an antioxidant, but as a strong pro-oxidant (Alloway 2013).

Selenium-Glutathione Peroxidase (GSH-PO), together with vitamin E, plays an important role of protection of biological membranes against damages provoked by

Lipid Peroxidation (LPO), reducing peroxides to alcohols (Dini et al. 1981). Toxic amounts of Se, moreover, provoke a noteworthy reduction of GSH, which is an active protector of haemoglobin. Elevated Se doses, furthermore, may interfere with embryo development, since Se is capable to cross the placental filter, reducing oxygen and energy availability.

Selenium carcinogenesis is a very debated problem. Prolonged assumption of small quantities of Se induced hepatic carcinomas and adenomas (Volgarev and Tscherkers 1967); however, recent advances assign to Se a major role in prevention of human neoplasms. Selenium supplementation has been reported to protect against various forms of cancer (prostate, colorectal, lung and liver) in prospective clinical trials from the United States and China (Alloway 2013). These data are consistent with earlier epidemiological studies, especially geographical ones from the United States, showing that mortality from several, but not all forms of cancer, and also from cardiovascular diseases (especially coronary heart disease and hypertension) was negatively correlated to the intake of Se (Alloway 2013).

Selenium poisoning may occur in both acute and chronic forms. Acute forms occur when huge amounts of Se compounds are taken in; symptoms are rapid and weak pulse, shortness of breath, bloating, intense colic pains, diarrhoea, poliuria, respiratory paralysis followed by death. Chronic forms (formerly "alkali disease" originating by excessive consumption of alkaline water) are due to ingestion of Se-contaminated food; symptoms are weight loss, anaemia, joint injury. Selenosis diagnosis is based on blood-Se up to 25 mg kg^{-1} in acute forms, and 2–5 mg kg^{-1} in chronic ones. Arsenic administration in diet is considered effective for chronic selenosis, while no intervention is effective for acute toxicity.

Selenium is known also for its counteracting effect on other metals: high plasma Se concentrations have been shown to decrease lead toxicity (Chuang et al. 2007). Selenium binds with toxic metals, reducing or eliminating their effect (Xie et al. 1998). Animal experiments have shown that Se at high intake levels has a strong protective effect against the toxicity of several calcophilous toxic metals, such as Hg, Cd and Ag (Alloway 2013). Its antioxidant effect may also be an important factor that reduces lead toxicity. Age is a well-established risk for impaired hearing ability, as well as Pb and Se were significantly associated. However, Se concentration was inversely associated with hearing thresholds: it might have a protective function for hearing. No synergistic effect was found (Chuang et al. 2007).

Recent studies and epidemiological observations on HIV progression confirm that Se and GSH directly affect the rate of HIV viral replication in patients. Enhanced oxidative stress (e.g. because of other infections) or impairment of the cellular capacity for antioxidant defence will therefore be a direct cause of progression from AIDS to HIV and mortality (Alloway 2013).

HIV-1 infection most likely occurs in subjects with poor diets; thus, maintaining an optimal Se status in HIV-1 patients may help to increase the enzymatic defence and reduce their risk of hospitalization (Roman et al. 2014). With increasing recognition of the role of antioxidants in disease prevention, the need for accurate determination of selenium status has become more important. Very few papers have

been published on the determination of selenium in hair, which allows long-term exposure to be monitored.

2.1.6 Chromium

Among heavy metals, up to now chromium has received little attention in comparison to, for instance, Cd, Pb, As and even Se. The reasons for this lack of interest are diverse. One is that Cr was considered a "local source" contaminant, thus not constituting a widespread environmental problem; nevertheless, because of lax regulatory guidelines, disposal of Cr-containing wastes over large areas has led to the present extensive contamination of soils in many parts of the world. A second reason is that the dominant naturally occurring form of Cr ~~in~~ the trivalent oxide chromite, which has a very stable crystal structure. Consequently, it is very slow to react and is considered essentially immobile in the environment. In contrast, Cr^{VI} is highly mobile and is considered acutely toxic, although its occurrence is rare in nature (Bini et al. 2000). Chromium has been recognized as an essential microelement for animals and humans, potentiating the action of insulin and therefore being effective in carbohydrate and lipid metabolism (Steinnes 2009). On the other hand, recent works point to the severe toxicity of Cr^{VI}, a form utilized in several industrial activities (electroplating, chemicals, varnish, leather tanning), with respect to human health. Indeed, it is known to be a skin irritant and to induce allergic contact dermatitis. In addition, Cr^{VI} has been recently determined to be a potent human carcinogen for which there is adequate evidence of carcinogenic risk (Wang et al 2011). Conversely, the reduced form, Cr^{III}, is considered to have low acute and chronic toxicity, mostly because of the demonstrated low capacity to penetrate animal cell.

The chromium concentration in soils is largely determined by the parent material; the average world Cr concentration in soils is 40 mg kg^{-1}; the highest Cr level (up to 1,800 mg kg^{-1}) is found in serpentine soils, the lowest (<10 mg kg^{-1}) occurring in calcareous soils (Adriano 2001).

Chromium is considered to be a not essential element in plant metabolism, and moreover it is slightly available to plants. The form most available to plants is Cr^{VI}, which is the very unstable form under normal soil conditions (Kabata-Pendias and Mukherjee 2007), and is acutely phytotoxic (Bini et al. 1999). However, it is not easily translocated within plants (Fontana et al. 2011); there is evidence that it is concentrated mainly in roots, that act as a barrier (Bini et al. 2008). Also Cr^{III} seems to be available to plants, accumulating in roots and leaves, where it causes chronic damage to cell structure (Maleci et al. 2014). Visual symptoms of Cr phytotoxicity are stunted growth, poorly developed root system, discoloured leaves (Kabata-Pendias and Mukherjee 2007). However, under normal field conditions phytotoxicity is unlikely to occur.

In contrast to plants, chromium is essential for normal energy metabolism of humans and animals, but above certain concentration levels it is toxic and ~~carcinogen.~~ It is reported to control the metabolism of glucose and lipids, and affects some

of the enzymes that regulate cholesterol synthesis with beneficial impact of Cr on cholesterol fractions (Kabata-Pendias and Mukherjee 2007). Inhalation is the main pathway Cr enters the human body: the respiratory tract is the major target organ for both acute and chronic exposures, which produce nasal ulceration, perforation of septum, bronchitis and other respiratory effects, and ultimately nasal and lung cancer. Oral Cr intake (food ingestion) is another way of exposure, that affects the gastro-intestinal tract; Cr^{VI} is more easily absorbed by the intestinal mucosa than Cr^{III}; however, in the case of Cr^{VI} ingestion, it is almost completely reduced to Cr^{III} by acid gastric juice in the stomach, thus reducing drastically the toxic effects likely provoked by Cr^{VI} (Adriano 2001).

The average daily intake for general population is estimated to be approximately 60–75 μg Cr, depending on age, gender, life style. Excessive doses of Cr intake have been associated with renal dysfunctions (Steinnes 2009), and may result in liver and kidney failure, anemia, muscle breakdown and abnormalities in blood clotting. When an excess of Cr compounds are inhaled, lung, nasal and possible stomach cancer may develop (Kabata-Pendias and Mukherjee 2007). Association between Cr inhalation and mortality due to lung cancer has been found in epidemiological studies; mortality from lung cancer is apparently influenced by cumulative exposure (Steinnes 2009). Chromium dermal absorption also is frequent; Cr is generally considered to be the second most common skin allergen after Ni, and produces increased sensitivity, skin ulceration and allergic contact dermatitis. Instead, increased cholesterol levels, high blood sugar levels, coronary dysfunction, arteriosclerosis and abnormalities of nerve stimulation may occur with Cr deficiency (Steinnes 2009).

In conclusion, as previously stated, Cr^{III} is an essential element to humans and animals, while Cr^{VI} is not, and act as a potent carcinogenic, especially in occupational setting. Thus, Cr^{III} and Cr^{VI} have contrasting relevance in biological systems: the former is an essential nutrient, while the latter is a toxin (Adriano 2001).

2.2 *Emerging Harmful Elements*

2.2.1 Aluminium

Aluminium is the third abundant element in the earth's crust, being a fundamental component of silicate rocks, where it may attain 8 %. Al-oxide (bauxite) is the most important aluminium ore, widely diffused especially in tropical areas. Aluminium is also an abundant element in soils, where its contents vary commonly between 1 and 4 % (Kabata-Pendias and Mukherjee 2007). Due to its versatile properties, application is current in different industrial sectors, including metallurgical, electrical and chemical, packaging, paper manufacturing, wood preservation and many others.

The total Al content of soils is mostly inherited from parent rocks and from new mineral species formed during pedogenetic processes; its distribution in soil

profiles is highly governed by chemical-physical conditions, organic matter, pH, and other soil properties. Only easily mobile and exchangeable fractions of Al play an important role in soil fertility. The mobile Al in acid soils can be taken up by plants and it creates a problem of chemical stress in plants. The most important problem is associated with Al toxicity, as one of the major factors which limits the growth and yield of plants cropped on acid (pH $<$ 5) soils. Al toxicity in soils is particularly harmful because it causes shallow rooting, drought susceptibility, and deficient nutrients input (Kabata-Pendias and Mukherjee 2007). Conversely, there is some evidence that low levels of Al may have a beneficial effect on plant growth.

Once considered as a not toxic element for human population, in early 1970s the scientific literature started to consider some toxicity evidences induced by Al as collateral effects of renal dysfunction treatment (dialysis), with intestinal Al absorption up to 500 mg. More recent research indicates Al as one of the factors directly related to neurotoxic disturbances (haedache, epilexy). No definite conclusions have been given on chronic Al exposure; however, aluminium is known to be neurotoxic at high exposure levels, (Steinnes 2009). Indeed, he long-term uptake of aluminium is implicated in the aetiology of neurological disorders such as Alzheimer syndrome (Polizzi et al. 2002) and arteriosclerosis (Nriagu 1988). The World Health Organization (WHO 1996) indicates that an excess A1 also seems to cause softening of bone.

Although there is much debate on Al effects on humans, so far no positive conclusions have been made, and the relation between A1 and Alzheimer's disease is still controversial (Kabata-Pendias and Mukherjee 2007).

Water is the main pathway by which A1 enters the human diet. The WHO (1993) guideline for A1 concentration in drinking water is 0.2 mgL^{-1}. A statistically significant association of Al in drinking water with the incidence of dementia was found (Steinnes 2009), although Al usually contributes a very small proportion (15–20 mg/day) of daily human intake, at the limit value of 1 mg Al kg^{-1} BW (WHO 1993). Yet, the major part of a typical daily intake comes from food (e.g. eggs 0.5–1 mg kg^{-1}; lettuce 5 mg kg^{-1}; meat 1–10 mg kg^{-1}), beverage (beer, tea) and food additives, with possible increase (up to 50 mg/day) due to the use of pans and other kitchen utensils made with aluminium. Considering a daily intake of Al, no risk is expected from eating food cooked in Al-pots and/or Al-foil. A minimal risk level for oral exposure of 2 mg Al kg^{-1} BW per day has been set up in the USA (Kabata-Pendias and Mukherjee 2007).

2.2.2 Antimony

In contrast to arsenic, which belongs to the same periodic group and have the same oxidation states, there is limited understanding of the behaviour, ecotoxicology, and the extent of environmental dispersion of antimony (Liu et al. 2011). Antimony is non-essential for human life, and is completely absent in living organisms; it is found in biological specimens from persons who have been exposed to industrial sources of antimony. Indeed, it is emitted into the environment through human

activities such as mining, smelting, alloys, emails, and the combustion of fossil fuels, and its concentration in the environment has increased by 50 % since the early nineteenth century. Although many investigators have highlighted the importance of the environmental chemistry of antimony (and bismuth) (Liu et al. 2011 and references therein), little information is available on how antimony contamination affects exposed populations. Pentavalent antimony is less toxic than trivalent antimony. In humans trivalent antimony is taken up by the red blood cells, whereas pentavalent antimony remains in the plasma and is more easily excreted than the trivalent form (Rahman et al. 2000).

Antimony has been classed as a priority pollutant by the United States Environmental Protection Agency (US EPA). The most likely route in the body from industrial exposure is from inhalation, or from ingestion of drugs containing the element, whose main medicinal use is in the treatment of parasitic diseases (Rahman et al. 2000). A study of industrial occupational exposure in the vicinity of the largest Sb mine in the world, in China reported mean antimony values of 0.05, 0.57 and 0.36 μg/g in hair from locomotive shed workers, industrial welders, and students and office workers, respectively. High antimony concentrations ($\geq$3 μg/g) were found in 80.0 % of children (5–9 years) and 69.6 % of adults aged 41–51 years (Liu et al. 2011).

In France, Sb intake was determined by consumption of goose liver (*foie gras*), achieved administrating to gooses 60 mg kg^{-1} day^{-1}antimony sulphide (today prohibited), which induced liver steatosis, and a Sb concentration up to 100 mg kg^{-1}.

Long-term intake of small amounts of Sb may induce chronic antimony poisoning. Sb exposure has been shown to induce DNA damage and oxidative stress, and generates reactive oxygen species (ROS), causing apoptosis; since Sb geochemical behaviour is similar to As, it is likely that the DNA damage induced by Sb follows similar pathways as those for As (Franco et al. 2009).

Limited information is available as to what level of antimony in hair can be used to estimate whether individuals are suffering from Sb chronic poisoning. Some studies have found that hair As levels are <3 μg/g. Consistently, 3 μg/g have been proposed by Liu et al. (2011) as the normal hair antimony level. Lethal Sb dose for humans (70 kg body burden) is estimated within 100 and 500 mg.

2.2.3 Beryllium

Beryllium is a very rare element (2–10 mg kg^{-1} in the earth crust). It is increasingly used in aircraft and spatial vehicles industry, as a hardening component in Al-Cu alloys, and as neutron source in nuclear reactors. However, the primary environmental source of Be is coal combustion, producing around 180 tonnes $year^{-1}$ (Adriano 2001). Beryllium is recognized as phytotoxic, but its availability in low amounts may have beneficial effects on plants, stimulating growth. It accumulates primarily in roots, and afterwards may translocate to aerial parts and accumulate in leaves. Deleterious effects are antagonism of nutrients such as Ca and Mg, and

inhibition of certain enzymes. It may enter the food chain through crop produce contaminated by industrial particulate matter. A second pathway of Be assumption is via drinking water; in three of 96 examined mineral waters a Be concentration above 3.0 μg L^{-1} have been determined (Cerutti, personal communication). AU3

Be, as well as Ag, As, Cd, Hg, Pb, are good examples of PHEs that have no proven essential functions in humans, and are known to have adverse physiological effects at relatively low concentrations (Abrahams 2002). Indeed, beryllium is highly toxic to living organisms, and affects exposed workers; the target organs are bones, liver, kidney, and lung. Pulmonary diseases that affect Be-workers are particularly serious, and may appear after long time from exposure. Be may induce also rickety, due to the high insolubility of Be-phosphate. Be-induced apoptosis has also been ascribed to ROS generation, but may be prevented by superoxide dismutase (SOD) mimics; Be also induces activation of protein kinase C in a ROS-independent manner (Franco et al. 2009).

Current data on Be effects to humans is lacking; more attention should be paid to this emerging element.

2.2.4 Bismuth

Bismuth is an emerging metal belonging at the same group as As and Sb, and the most common chemical form is sulphide; large ore deposits are found in southern America, Australia and northern Sweden. Its geochemical behaviour may be compared with that of As and Sb. Although little investigated, it is known since ancient times, and the main usage is in easy fusible alloys with Pb and Sn, and in pharmaceutical industry, as substitute for Hg, being less toxic. Currently there is a great interest in some clinics for the monitoring of patients on bismuth drip treatment for peptic ulcer complaints (Rahman et al. 2000).

Industrially it is considered one of the less toxic heavy metals. Yet, the metallic form Bi is not considered toxic and poses minimum threats to the environment. Conversely, Bi compounds generally have very low solubility but they should be handled with care, as there is only limited information on their effects and fate in the environment, and the cautelative principle should apply.

The main routes of Bi entry in the human body are dust inhalation, skin contact and ingestion by food or drinking water. Exposure may cause both acute and chronic effects. The bismuth content in most biological samples is very low, with biological fluids normally containing only a few ng ml^{-1}, while in biological tissues concentrations may range from 10 to 90 ng g^{-1}. Jorgensen et al. (quoted in Liu et al. 2011) reported that bismuth concentrations ranged <0.03 to <0.1 μg/g in mammalian tissues. Hair is the target tissue for assessing Bi poisoning. Park et al. (2007) found a mean bismuth level of 0.04 μg/g in hair samples from 655 children (3–6 years old) from metropolitan and small cities in Korea. High bismuth concentrations (≥ 0.1 μg/g) were observed in individual groups of various ages affected by bismuth exposure. Children (5–9 years) and adults aged ≥ 41 years presented higher Bi levels than individuals in other age groups.

Toxic effects, both acute and chronic, have been recorded upon exposure to bismuth and its salts.

Acute effects determined by inhalation are a nuisance dust causing respiratory irritation. Inhalation may cause foul breath, metallic taste and gingivitis. Ingestion may cause nausea, loss of appetite and weight, albuminuria, diarrhoea, skin reactions, stomatitis, headache, fever, sleeplessness, depression, rheumatic pain and a black line may form on guns in the mouth due to deposition of bismuth sulphide. Skin contact and dermal absorption may cause irritation. Exposure to contaminated atmospheric particulate may cause eyes irritation (Lenntech BV – Internal report, 2013, unpublished. Delft, The Netherlands).

Bismuth Chronic effects: long-term Bi inhalation may affect the function of liver and kidneys. Ingestion, besides affect the function of liver and kidneys, may cause anaemia, black line on gums and ulcerative stomatitis. Skin contact and dermal absorption may cause dermatitis.

Although little information is available on Bi carcinogenicity, bismuth is not considered a human carcinogenic; nevertheless, it can cause kidney damage. Other toxic results may develop, such as vague feeling or bodily discomfort, presence of albumin or other protein substance in the urine, diarrhea, skin reactions and sometimes serious exodermatitis. Serious and sometimes fatal poisoning may occur from the injection of large doses into closed cavities and from extensive application to burns (in form of soluble bismuth compounds). Administration of large doses can be fatal. It is stated that the administration of Bi should be stopped when gingivitis appears, for otherwise serious ulceration stomatitis is likely to result.

2.2.5 Boron

Boron is a widely diffused light non-metallic element, that is easily available as H_3BO_3 (sassolite) in volcanic fluids in Tuscany (Italy) and as $Na_2B_4O_7.10H_2O$ (borax) in Tibet, Chile and California (USA). Boron compounds usage was recommended at very low dose as food preservative, but is currently prohibited in several countries because of its toxicity at doses of grams; the main industrial use is in glass, email and paints industry, soaps and teeth pasts preparation. As pharmaceutical it is a light antiseptic, and in agriculture, it proved efficient in enhancing flowering of orchards, and particularly the olive groves. Given its ability to form complexes with sugars, B has been implicated in sugar transport across cell membrane. Some plants (sesame, sugar beet) showed B accumulation in leaves as a consequence of passive transport from roots to shoots, *via* xylem, eventually up to a toxic level (Adriano 2001). Boron is essential for plant growth, although the amounts requested for some crops (e.g. alfalfa) may cause damage to other crops (e.g. legumes and cereals). Conversely, B deficiency has been reported in food crops in USA, UK and Australia, without apparent geographic pattern. Concentrations <0.05 μg B mL^{-1} proved to produce deficiency, while 1.0 μg B mL^{-1}proved toxic; 0.50 mg kg^{-1} is likely a safe level, while ranges 0.05–0.10 μg B mL^{-1} look

adequate for many plants. For example, sunflower, cotton, celery, cauliflower are more sensitive in comparison to cabbage, broccoli, carrots, clover, radish, olive (semitolerant), and to tolerant plants such as corn, oat, onion, potato. High boron levels in irrigation water may cause a rise of boron levels in the soil to a toxic extent. Tolerant crops may achieve 2.0–4.0 μg B mL^{-1} before presenting toxicity symptoms (e.g. chlorosis), while USEPA has set a limit of 0.75 μg B mL^{-1} for long-term irrigation water.

From plants, B may enter the food chain. To date, there is no sufficient information on the essentiality of B in animal nutrition and human health, and also its toxicity has not been established conclusively (Steinnes 2009). The World Health Organization Committee on Trace Elements in Human Nutrition (WHO 1996) concluded that B is *probably essential*, being beneficial in humans and animals for many life processes as cell membrane function, mineral and hormone metabolisms, and enzyme reactions (Kabata-Pendias and Mukherjee 2007). The only information is that excessive boron intake (4,000 mg day^{-1}) may cause symptoms of boron poisoning, such as gastrointestinal disturbances, skin eruptions, and signs of central nervous system stimulation, followed by depression (WHO 1996).

2.2.6 Copper

Copper is known since the pre-historical times, and gives the name to an epoch of civilization; Greeks and Romans exploited Cu from Cyprus (its Latin name *cuprum* comes from there) and Spain, and commerce flourished with copper, as well as with lead. Native Cu and Cu compounds come from Chile, USA, Russia, Africa; mixed sulphide with Pb, Fe, Zn were exploited until the 1960s of the last century in several countries, including Italy (Bini 2012; see also this volume, Chap. 5). Copper is the most widely used metal in the world, after iron. Its usage is mainly in electrical applications and energy transport (42 %), metallurgy (33 %), agrochemicals (12 %), and others.

Copper is an essential microelement to living organisms, contributing to haematopoietic function and to the formation of bone tissue. Moreover, it is a component of several important enzymes acting in oxidation-reduction processes and in catalysis of enzymatic reactions such as urease, laccase, hydroxylase. Copper is considered slightly toxic; Cu-poisoning may occur as a consequence of excessive Cu intake from the food chain (e.g. from pesticide-contaminated forage, vegetables and particularly vineyards treated with the classic "Bordeaux mixture" based on copper sulphate). Yet copper, unlike lead, is largely absorbed by plants growing on naturally enriched soils or in areas conterminous to industrial plants (smelters) and mines, or spread with sewage sludge and as antiparasitic and fungicide in agriculture.

Copper is essential for man; it forms organic complexes, and metalloproteins, especially haemoglobin. Some function as enzymes in metabolic reactions. Copper aids blood clotting, maturation of connective tissue, development of the bones, and participates in lipid metabolism (Davis and Mertz 1987). The metabolic behaviour

of Cu is strictly connected with that of Mo. This metal, indeed, enhances copper elimination from liver, and counteracts, as well as other metals (Fe, Zn, Cd) its absorption in the gastro-intestinal tract, at amounts less than 30 % of the ingested Cu. The ingested copper dissociates and forms new Cu-complexes with amino acid as carriers of active transport crossing the intestinal mucous; within the cells, it binds metallothionein and than enters the circulatory system; in the plasma, it may bind albumins or is distributed in cytoplasm and in different subcellular fractions, where enzymatic synthesis occurs.

Similarly to other essential (and critical) elements, both Cu-deficiency and excess may occur, and the pathways of exposition are inhalation, ingestion and skin contact, the latter being common with workers in agriculture; however, ingestion of contaminated food is the most likely to occur.

An intake of 2 mg Cu day^{-1} is assumed to be adequate for healthy adults, 80 pg $day^{-1}$for infants and 40 pg day^{-1} for children (Oliver 1997). Deficiency is generally induced by inadequate diet, especially in developing countries. Toxicity from Cu excess is rare: the WHO (1996) suggests a safe upper limit of 12 mg day^{-1} for adults and 150 pg day^{-1} for children.

Copper deficiency in humans is serious and may lead to typical disease symptoms such as anaemia and leukopenia, bone deformations, osteoporosis, lack of colour of the hair and skin, degeneration of the hearing muscle, reduced elasticity of arteries, coronary heart disease, and neurological disorders. Antagonistic effects with Mo are reported (Steinnes 2009). Deficiency is associated with anaemia and neutropenia in premature babies, and with diarrhoea in children (Oliver 1997).

Excessive Cu intake induce acute and chronic toxicity, although with generally mild forms. Acute poisoning may be determined by Cu intake up to 200 mg kg^{-1}; more complex is quantification of chronic poisoning, given the interaction/counteraction with other metals; for example, it is considered to be harmful a diet with a ratio Cu/Mo less than 10:1. If ingested at high amounts, copper acts as a protoplasmatic poison with regard to the gastro-enteric tract mucous. The long-term intake of Cu normal doses may determine metal accumulation in liver, provoking functional and structural alterations symptomatic of incipient poisoning. However, no carcinogenic effects are recorded with copper. Once overcome a certain accumulation level (e.g. 150 mg kg^{-1}), liver releases a huge amount of metal, and possibly oxidant substances in the circulatory system, with red globule membrane damage (LPO), determining haemolytic crisis. Indeed, copper is prone to participate in the formation of ROS, leading to final LPO and cell apoptosis (Franco et al. 2009).

Acute poisoning symptoms, as for other metals (e.g. Hg, Pb, Tl) are generally vomit, colic pains, diarrhoea with fluid greenish faeces, cardio-circulatory collapse, and death is likely to occur. The lethal dose for humans is considered to be 2.5 g/70 kg body weight.

Similar critical evolution occurs also with chronic poisoning; symptoms are weakness, muscle tremors, haemoglobinuria, jaundice, dyspnea. Liver is generally hypertrophic, kidney presents necrotic tubular alterations, that may induce

degenerative phenomena in the brain. Morbidity of chronic poisoning is generally low (<5 %), while mortality is high, with 75 % of subjects dying within 3–4 days.

Chronic poisoning may be assessed by the quantitative estimate of blood-Cu, whose physiological amount is in the range 1–3 mg kg^{-1}. Poisoning prevention may be achieved with equilibrated administration of NH_4-molibdate.

2.2.7 Fluorine

Fluorine is a very reactive element (most of the halogen group) and may combine with several other elements, including inert gases. Fluorite (CaF_2) is the most common commercial source of F. It is used the Al-industry, in the steel industry, and also in plastic, ceramic and glass production and in various chemical processes (Kabata-Pendias and Mukherjee 2007).

Fluoride has long been added to municipal drinking water (at the level of 1.2–1.9 mg L^{-1}) for the prevention of dental caries. It is still added to tooth pastes.

Elemental fluorine does not pose severe poisoning hazard to living organisms, while both organic and inorganic compounds play a significant role in toxicology, being frequent in nature, associated with P-bearing minerals. Soils derived from P-bearing rocks contain huge amounts of F; however, it is not easily translocated to plants, being arrested mostly in roots. The main source of fluorine is from industrial plants such as smelters, foundries, glass factories, aluminium and steel produce, whose emissions (both fumes and dust) are dispersed in conterminous areas, contaminating soils and vegetation. Contamination, therefore, results from the site topography and from wind regime.

Environmental pollution by F in some regions has become of ecological importance. The reactions of plants exposed to F pollution, before any visible toxicity symptom, are retarded growth, inhibited reproduction, and yield reduction. However, the greatest concern with increased F concentrations in plants is related to the toxicity to mammals, including humans (Kabata-Pendias and Mukherjee 2007). The average F contents in mammalian tissues are established as 2–5 mg kg^{-1} in soft tissues and 250 mg kg^{-1} in the skeleton, where F substitutes for (OH) in the mineral structure of teeth and bones. Fluoride ion F^- is able to bind and precipitate the essential ion Ca^{2+}, decreasing its physiological functions, and in particular inhibiting enzymatic activity and arresting cell respiration. Dental fluorosis affects developing teeth with thinning of the layer of enamel and dentin defective mineralization. Bone lesions are a consequence of inadequate formation of bone matrix and subsequent deficient mineralization.

Exposure to fluoride may occur by ingestion, inhalation or by skin absorption; the oral pathway is the prominent, and fluoride absorption by the gastro-intestinal tract is very rapid, although the occurrence of Ca, Al, Mg, Fe, P counteracts F^- absorption. Fluoride distribution in the animal body is mostly in hard tissues (skeleton and teeth) and secondly in kidney, although it has been found in all organs and tissues. Excretion is generally via renal system; by interrupting exposure, F^- depletion occurs very slowly, in several months or even years.

Recently there has been a wide discussion on the health risk associated with increased intake of F. Fluorine toxicity may occur both in acute and chronic form, in relation to ingested amount, exposition, absorption capacity in bones and teeth. Threshold levels are considered to correspond to a daily intake up 40 mg kg^{-1} NaF; however, with only 15 mg kg^{-1} dental alterations may occur. Severe toxicity and bone lesions have been observed within 30 days after intake of 100 mg kg^{-1} NaF; lethal doses are achieved with intake 100 g (Beretta 1984). The intake of 20–70 mg F day^{-1} by adults can cause heartburn symptoms due to displacement of Ca.

Elevated F levels in drinking water can produce both mutagenic and carcinogenic changes in the kidneys. It has been observed that the mortality rate from cancer in the cities using fluorinated water increased significantly as compared with the cities that did not use fluorinated water. Consistently, in several countries, F addition to drinking water has ceased, although in the last century there has been great interest in the fluoridation of water as means of reducing dental caries (Kabata-Pendias and Mukherjee 2007). Dental tissue also shows the earliest sign of toxicity; concentrations of F over 1 mg L^{-1} are likely to produce symptoms, and mottling of the teeth is prevalent when the concentration exceeds 4.5 mg F L^{-1} (WHO 1996). Nearly one million people in rural India suffer for fluorosis, a chronic, incurable, and debilitating affliction (Oliver 1997). Moderate amounts of F are beneficial to dental structure, whereas intake of high amounts may lead to development of dental fluorosis, and in extreme cases skeletal fluorosis.

Although no cases of F deficiency have been reported in humans, some symptoms of low F supply have long be linked to dental decay, osteoporosis, and possible with growth retardation (Steinnes 2009). These symptoms are observed mainly in children <6 year age.

Typical symptoms of intoxication (fluorosis) are mottling of tooth enamel and several skeletal and joint deformation including spinal curvature and knock-knees problems. Some individuals may be especially susceptible to F and its compounds. These include elderly people, persons with deficiencies of Ca, Mg, and vitamin C, as well as people with cardiovascular and kidney problems (Kabata-Pendias and Mukherjee 2007).

Acute fluorine intoxication is characterized initially by gastro-enteric disturbances, vomit, abdominal pains, diarrhoea, as a consequence of gastro-intestinal mucous irritation. Afterwards, muscle tremors, urinary incontinence, cardio-circulatory collapse may occur owing to hypocalcaemia. Respiratory paralysis and heart failure determine lethal consequences.

Chronic intoxication is the most frequent, and is characterized mostly by evident disturbances of skeletal apparatus during a time span ranging from 6 to 12 months. The process starts with scarcely relevant bone lesions, and proceeds with thickening of the long bones of the limbs, calcification, spontaneous fractures. Dental lesions too (e.g. partial enamel loss, teeth erosion) are a sensible index of chronic intoxication, with possible infection of oral cave. Chewing is more and more difficult and painful, and this is reflected on the nutritional state and the growth retardation. Urinary excretion may be accompanied by the reduction of blood levels of goitre hormone, determining hypothyroidism, anaemia, leucocytosis.

An improvement of the fluorosis disease may be obtained by administering in the diet Ca-salts and especially Al-salts, that reduce fluorine bone content by 45 %. Fluoride tolerance may be augmented by equilibrated assumption of Ca, P, vitamin D.

2.2.8 Iodine

Iodine has an extreme variability in the earth's crust, with the highest content in sedimentary rocks (1.5 mg kg^{-1} in shale), and the lowest in volcanic rocks. Its concentration in surface soils is generally higher than the corresponding parent material, and the suggestion of an atmospheric origin of I seems to be most reasonable. Iodine and its organic compounds are utilized in a number of chemicals and pharmaceutics, both for external and internal applications. Radioactive isotopes are most commonly by-products of atomic reactors and are used in medical diagnosis; being released in various proportion into the environment, they are of growing environmental and health concern (Kabata-Pendias and Mukherjee 2007).

Iodine was the first element to be recognized as essential to human health, in 1846 (Oliver 1997). It has long been known as an essential element for humans and mammals, where it is a component of the thyroid hormone thyroxin (Steinnes 2009). This contains up to 80 % of the total body store of I and is involved in most biological processes (e.g. bone growth, reproduction). Therefore, an adequate level of I in the human body is crucial (Kabata-Pendias and Mukherjee 2007).

The daily requirement of I by adults is around 150–200 μg. Intake below 100 μg day^{-1} has resulted in mild deficiency, and a dose below 20 μg day^{-1} has caused severe deficiency symptoms (Kabata-Pendias and Mukherjee 2007).

Insufficient supply of I (*hyperthyroidism*) may lead to a series of iodine deficiency disorders, the most common being endemic goitre, which was the first endemic disease attributed to the environment. Goitre was first recognized as resulting from I deficiency in areas far from the sea and in the Alps and Himalayas.

Iodine deficiency during pre-natal development and the first year of life can result in endemic cretinism, a disease that causes stunted growth and brain damage. Other consequences of I deficiency include abortions, stillbirths, congenital abnormalities, impaired mental function and reduced thyroid hormones. Of these the most serious disorder is endemic cretinism (Oliver 1997) which is caused by the most severe I deficiency. Goitre occurs when I intake is 50 % of normal (WHO 1996). Hyperthyroidism is generally counteracted administrating more (radioactive) I to patients. The only common side effect of radioactive iodine treatment is underactivity of the thyroid gland. The problem here is that the amount of radioactive iodine given kills too many of the thyroid cells so that the remaining thyroid does not produce enough hormone, a condition called *hypothyroidism*. There is no evidence that radioactive iodine treatment of hyperthyroidism causes cancer of the thyroid gland or other parts of the body, or that it interferes with a woman's chances of becoming pregnant and delivering a healthy baby in the future. It is to note,

moreover, that women are more prone to hyperthyroidism than men, and that this disease affects more frequently older individuals than young persons.

2.2.9 Cobalt

Cobalt, as well as manganese (see below) are two heavy metals which have received little attention in comparison to other heavy metals such as lead and cadmium, for example. Their lack of notoriety is a result of their lower potential to exert any toxic properties that they may have and to the lack of appropriate situations, particularly in soils (Alloway 2013). Nevertheless, they play significant roles in soil health, acting as oxidants and Co, in particular, for medical treatments. Indeed, the only known Co function is as a constituent of Vitamin B12, which plays a major part in animal cells; its deficiency in humans causes pernicious anaemia and severe effects on the nervous system.

Cobalt occurs in all mammalian tissues and its contents vary from 5.5 to 230 μg kg^{-1}, with the highest value in the liver and the lowest in the brain. Although inorganic Co is present in several organs and tissues, its possible other physiological functions are unknown. Cobalt is likely to be bound by some proteins and to replace other divalent cations (e.g., Zn, Mn) in various enzymes, without any effects. Some organic Co compounds are apparently involved in processes of stabilizing the DNA structure (Kabata-Pendias and Mukherjee 2007). Co has also been observed to induce ROS and apoptosis in different cell lines, leading to oxidative DNA damage via OH^- formation (Franco et al 2009).

Cobalt deficiency in living organisms refers to the scarcity of Co in soils (0.30 mg kg^{-1} in severely Co-deficient areas, according to Adriano 2001) and may affect the animals' health, when pasture concentration falls below 0.08 mg kg^{-1}. Conversely, the occurrence of Co contamination of soils is rare (up to 1,000 mg kg^{-1} in serpentine soils), as well as Co toxicity, except in particular circumstances.

The deficiency of Co may affect anaemia and anorexia. The excessive ingestion of Co may cause polycythemia (increased red blood cells), cardiomyopathy, hypothyroidism, pancreas failure, bone marrow hyperplasia, and some types of cancer.

Human dietary intakes of Co vary from 5 to 40 μg day^{-1} and is mainly from the ingestion of foods, particularly from livers and meet products (Kabata-Pendias and Mukherjee 2007).

2.2.10 Manganese

Manganese, as well as Co (see above) is an heavy metal which has received little notoriety in comparison to other heavy metals such as lead and cadmium, for example. The lack of notoriety is a result of its low potential to exert any toxic properties, and to the lack of appropriate situations, particularly in soils.

Nevertheless, the ability of Mn oxides to absorb preferentially heavy metals and to act as oxidants means that it plays a significant role in soil health (Alloway 2013).

Both Mn deficiency and toxicity occur in plants and Mn may be of environmental concern in a few situations associated with water quality and the mining of Mn ores.

Mn is an essential element for humans and is considered an element of low toxicity. Its physiological function is closely associated with some enzyme activities, (e.g. superoxidase, dismutase, arginase) and with metallothionein. It is also known that Mn^{2+} is involved in gene expression processes and stabilizes the DNA structure (Kabata-Pendias and Mukherjee 2007).

In general, Mn is an activator of different enzymes that control the metabolisms of carbohydrates, proteins and lipids (including cholesterol), and nitrogen metabolism. Moreover, it affects the functioning of other enzymes which are involved in bone formation.

The most common Mn deficiency symptoms in livestock are impaired reproduction, skeletal deformities and shortened tendons in the newborn; in humans it can also cause impaired insulin production, lipoprotein metabolism, oxidant defence and growth factor metabolism (Alloway 2013), and neurological disturbances (Iregren 1990).

A great proportion (over 50 %) of Mn in the human body is located in the hepatocyte nuclei of liver, likely indicating some functions of this metal in genetic regulation (Kabata-Pendias and Mukherjee 2007, and references therein). The Mn contents in human tissues, especially in bones, decrease with age; this can be associated with skeletal deformities and bone fractures (osteoporosis), dermatitis and hypocholesterolemia. Moreover, testicular dysfunctions can result from a Mn deficiency.

Manganese deficiency in humans has also been associated with the incidence of esophageal and other types of cancer (Steinnes 2009). However, symptoms of Mn deficiency in humans are very rare.

The adequate daily intake of Mn by adults was previously given to be between 2 and 6 mg day^{-1} whereas the recent USEPA recommendation is up to 10 mg day^{-1} for a 70 kg body weight.

Of the three pathways of Mn exposure, the most harmful is inhalation. Oral Mn poisoning has not been recorded often and is mainly related to drinking water. The ingestion of excess Mn by food may result in liver cirrhosis. The inhalation of Mn-rich dust by humans can increase susceptibility of the respiratory tract to infection and can induce Mn-pneumonitis and some neurobehavioral impairment (Kabata-Pendias and Mukherjee 2007). Mn, together with As, has also been suggested as ototoxin affecting hearing (Chuang et al. 2007).

2.2.11 Molybdenum

Molybdenum occurs at relatively low concentrations in most rocks and soils, but in relatively high concentrations in soils developed on black shales (Abrahams 2002).

It is most mobile and plant available in alkaline conditions. It is primarily used in metallurgy for producing various alloy steels and stainless steel, aircraft and automobile components, cutting tools, support wires for filaments in incandescent light bulbs, catalysts, lubricants, pigments and other uses (Alloway 2013).

Concentrations of Mo in soils are generally the lowest of all the essential trace elements for plants (B, Cl, Cu, Fe, Mn, Mo, Ni and Zn). Sewage sludges commonly contain 5–50 mg Mo $kg^{-1}$and if high Mo sludges are applied to pastures they could cause *molybdenosis* problems in livestock. Yet, molybdenum-induced copper deficiency is a serious problem on Mo-rich pasture soils in several countries.

Besides its known essential role of micronutrient for plants, Mo has recently proved an essential element for both animals and humans. Normal Mo concentrations in plant leaves are 1 mg kg^{-1} or less; plants growing on contaminated soils have been reported to contain <200 mg Mo kg^{-1} (Steinnes 2009). On a global scale, deficiency of Mo in crops is more important than potential excesses from contamination because it is essential to plants. Nevertheless, deficiencies can occur in *Brassicaceae*, legumes, wheat, sunflower and some other crops in many parts of the world, mainly on acid and sandy soils (Alloway 2013).

In animals, Mo is required for the functioning of several enzymes involved in transformations of C, N and S. In grazing livestock, a close connection between Mo, Cu and S is involved in molybdenosis, which is a Mo-induced Cu deficiency. (Alloway 2013). However, deficiency cases are rare. The only people known to have Mo deficiency are those with a genetic defect which prevents the synthesis of sulphite oxidase and causes severe illness except when Mo is administered. Symptoms included tachycardia, headache, nausea and vomiting (Kabata-Pendias and Mukherjee 2007). Sulphite oxidase is very important in humans because it is involved in the metabolism of S-containing amino acids and bisulphite preservative in foods (Alloway 2013).

The main dietary sources of Mo are legumes, nuts and grain products. Tissue concentrations of 0.03–0.15 mg kg^{-1} (dry weight) are considered to be adequate for nutritional requirements (Steinnes 2009). The excess Mo in the human diet influences its accumulation in serum, urea, and hair. With excess amounts, it may exert an antagonistic effect on Cu, causing a secondary copper deficiency.

Molybdenum is not considered as a carcinogenic element. However, there is still inconclusive epidemiological evidence that low Mo intakes may be associated with the occurrence of oesophageal cancer in humans. Apparently, it is also related to cancer of the stomach (Kabata-Pendias and Mukherjee 2007).

2.2.12 Nickel

Nickel is a transition element with a broad range of applications in modern industry, being used in everything from coins to automobiles to jewellery (Alloway 2013). The largest Ni use is by far stainless steel manufacturing. Moreover, Ni is an excellent catalyst for many reactions and so it is used for a large number of industrial and research applications alone or in combination with other metals.

Ni is well known as an essential trace element for plants and domestic animals, but has not yet proven to be essential to humans. Nickel in plants ranges generally from 0.05 to10 mg kg^{-1} dry matter. Nickel deficiency is very rarely found in plants, due to the very small amount needed for normal metabolism; symptoms of Ni deficiency, such as leaf tip and vein necroses, and patchy necrosis of younger leaves may occur (Gonnelli and Renella 2013).

With increasing Ni contamination, excess Ni is more commonly found in these organisms, and toxicity symptoms may occur. With regard to Ni toxicity to plants, threshold concentrations are commonly reported to be less than 100 mg g^{-1}. Responses to toxicity differ significantly according to plant species, growth stage, soil Ni concentration and exposure time. In general, critical toxicity levels are $>$10 mg g^{-1} dry matter in sensitive species, and $>$50 mg g^{-1}(dry matter) in moderately tolerant species (Alloway 2013). Among the toxic effects due to high Ni concentrations in plants, retardation of germination, inhibition of growth, reduction of yield, induction of leaf chlorosis and wilting, disturbance of photosynthesis (Gonnelli and Renella 2013) are the most common symptoms. However, there exist Ni-accumulator plants (e.g. the well known *Alyssum bertoloni*, a typical endemic of serpentine soils) that apparently do not show evidence of toxicity symptoms.

Ni-beneficial effects have been recorded in experiments with Ni-deprived animals. Nickel seems to be a bioactive element with some beneficial functions. Ni deprivation affects reproductive function in goats and rats, and changes carbohydrate and lipid metabolism. Nickel has beneficial effects in bone and may also alleviate Vitamin B12 deficiency (Gonnelli and Renella 2013).

Nickel is scarcely absorbed by human organism, with the exception of the respiratory tract in metal industry workers, since it may be released by Ni- bearing alloys (e.g. special steel widely used in food industry).

The Ni deficiency seems unlikely to occur in humans. However, Ni requirements by adults have been established as 25–35 μg day^{-1} (Kabata-Pendias and Mukherjee 2007). Lower Ni intake can induce some dysfunction of lipid metabolism, but human diets generally contain sufficient amounts of Ni. The usual Ni daily intake, comprehensive of the three pathways, is within the range 0.3–0.6 mg $day^{-1}$for humans (70 kg body weight). Legumes contain the highest Ni amounts (up to 1.60 mg kg^{-1} in peas), whilst it is nearly absent in milk, eggs and cattle meat. Normally, food assumption does not induce toxic effects. The optimum Ni intake should probably be $<$100 mg day^{-1}. and the average Ni intake by inhalation is calculated to range from 0.1 to 1 μg day^{-1}. Smokers inhale from 2 to 12 μg of this metal, for each pack of cigarettes (ATSDR 2002).

The toxicity of Ni is relatively low, but Ni allergy is a significant problem in humans, even at low exposure doses (Steinnes 2009). Instead, the toxicity and carcinogenicity of high doses of Ni are well documented and depend mainly on its potential to damage proteins and nucleic acids. Yet, Ni is known as producer of ROS (e.g. OH^{-}), lipid peroxidation (LPO) and oxidative DNA damage and, in addition, has been shown to induce NO production (Franco et al. 2009).

Investigations on the toxicity of Ni have indicated various effects of its excess, among which the most important are developmental, genotoxic, neurological,

reproductive, and carcinogenic (Kabata-Pendias and Mukherjee 2007). Slightly soluble Ni compounds, in particular, are likely to be carcinogenic at the site of deposition (ATSDR 2002). Toxicology concerns nearly exclusively the incidence of lung and respiratory tract cancer as professional disease of nickel refinery workers.

Therefore, Ni should be used with great precautions in industry since it is exceedingly toxic when inhaled. Moreover, sensitivity from Ni may occur also with dermal absorption (e.g. by bracelets and other fittings), causing allergenic dermatitis.

2.2.13 Thallium

Thallium is an actual poisonous heavy metal, and is a US Environmental Protection Agency (USEPA) priority pollutant. It was discovered in 1861 in Pb-bearing mud with which it has somewhat chemical affinity but, while being a highly toxic element, has been studied to a much lesser degree than other toxic elements such as cadmium or mercury, probably because classical analytical methods have less sensitivity for Tl than for other elements.

Besides current industrial uses in semiconductors, electronics, NMR, glasses etc., over 150 uses and potential applications for thallium and its compounds are recorded. In the past (since 1883), thallium was extensively used for medical purpose: in the treatment of venereal diseases, tuberculosis and malaria, to produce hair loss in the treatment of children ringworm (Peter and Viraraghavan 2005). The use of thallium salts as poisons for rodents and later as insecticides began in 1920 and for the next 45 years remained the principal use for this element (Nriagu 1988).

Thallium is normally associated with sulphide minerals and is often found in mineralized areas interspersed with sulphide deposits. Thallium pollution, therefore, is manmade; the most important anthropogenic sources of thallium are emissions and solid wastes from coal combustion and ferrous and non-ferrous smelting (Oliver 1997).

The ecotoxicological importance of thallium is derived from its high acute toxicity on living organisms, comparable to that of lead and mercury (Peter and Viraraghavan 2005). The major pathway of Tl exposure for animals and humans is the ingestion of plants grown in Tl-contaminated soils (Alloway 2013). A concentration range of 0.17–0.22 μg g^{-1}in garden soils, in Canada, and a range of 0.2–2.8 μg g^{-1}on various soils in the USA were reported (Ferguson 1990). In soils originating from a mining area southwest Guizhou, China, Tl concentrations ranged from 40 to 124 mg kg^{-1}, and from 1.5 to 6.9 mg kg^{-1} in undisturbed natural soils (Peter and Viraraghavan 2005).

The most widely documented case (Alloway 1995) was in West Germany near to a cement works, where Tl was deposited on the soil from the atmosphere. Crops grown on the contaminated soil showed significant amounts of Tl, and the people living there were poisoned by eating them. Many inhabitants suffered ill health, such as depression, insomnia and various nervous disorders (Alloway 1995).

Following that episode, in Germany, 1 mg kg^{-1} Tl in soils has been established as the tolerance level for agricultural use (Alloway 2013).

The contents of Tl in most mammalian tissues is reported to be <200 μg kg^{-1}, with level increasing at 500 μg kg^{-1} in skin (Kabata-Pendias and Mukherjee 2007). Mean Tl concentrations in human tissues and fluids range from <1–9 μg kg^{-1} and 0.2–0.4 μg L^{-1}, respectively. The median contents of Tl in kidneys and hair of healthy unexposed individuals have been reported as 0.5 and <1 μg kg^{-1}, respectively (Kabata-Pendias and Mukherjee 2007).

Although several hundred cases of acute and chronic thallium poisoning in man have been recorded, only a few cases resulting from industrial exposures have been reported. Intoxication mainly resulted from skin contact, since it is easily absorbed not only through the gastrointestinal tract but also through the skin. Exposure via inhalation may occur in the extraction of the metal, in the manufacture of thallium-containing rodenticides and thallium-containing lenses, and in the separation of industrial diamonds (Peter and Viraraghavan 2005).

Considering that exposure to high levels of thallium can result in harmful health effects for workers and general people, several World Organizations (e.g. OSHA, ACGIH, NIOSH) and Governments (e.g. in Canada, Russia, Switzerland, USA) have proposed a threshold limit value (TLV) of 0.1 mg/m^3 for thallium in work place air. Yet, a study on chronic health effect of workers exposed to Tl over several years reported nervous system effects, such as numbness of fingers and toes, from breathing thallium. Based on previous studies, the National Institute for Occupational Safety and Health (NIOSH) has recommended that 15 mg/m^3 of thallium be considered immediately dangerous to life and health. However, some studies indicated that there is no thallium mutagenicity or teratogenicity (Peter and Viraraghavan 2005).

Ingested Tl is also harmful to organisms. General exposure occurs through the food chain, especially from fruits and vegetables grown on contaminated soils (Kabata-Pendias and Mukherjee 2007). Accordingly, Swiss and Canadian Governments, established the maximum admissible level of thallium in agricultural soil at 1 mg/kg dry weight.

The toxicity of Tl has not been greatly studied, but its harmful impact has been observed in both humans and animals; moreover, Tl does not play any role in their metabolisms. It has been reported also that Tl is more acutely toxic than Hg, Cd, Pb, Zn and Cu in mammals (Peter and Viraraghavan 2005).

Initial thallium poisoning symptoms in humans are palmar erythema, acne, loss of hair and hallucinations. The principal features of acute thallium poisoning are gastroenteritis, polyneuropathy and alopecia (Kazantzis 1986, 2000). With acute intoxication, there is usually an initial hypotension and bradycardia, followed by hypertension and tachycardia. The central and peripheral nervous system is the main critical organ in thallium intoxication. Major symptoms of Tl poisoning include anorexia, headache, pains in abdomen, upper arms and thighs and even in the whole body. In extreme cases, alopecia, blindness and even death may be caused (Peter and Viraraghavan 2005, and references therein).

The mechanism of Tl poisoning is not very clear but, similarly to other trace metals, Tl binds sulfhydryl groups of proteins and mitochondrial membranes, thereby inhibiting a range of enzyme reactions and leading to a generalized poisoning (Kabata-Pendias and Mukherjee 2007). Possible toxic mechanisms of thallium include ligand formation with proteins, inhibition of cellular respiration, interaction with riboflavin (Vitamin B2), and distribution of calcium homeostasis (Peter and Viraraghavan 2005).

Thallium is excreted mainly through the urine. Thallium excretion via the kidney can be increased upon dosage of potassium chloride, potassium ferricyanoferrate (Prussian Blue) or employment of diuretics (Ghezzi and Marrubini 1979; Hoffman 2003). Hemodialysis and forced diuresis can be an effective means of decreasing the Tl body burden. Polyneuritic symptoms, sleep disorders, headache, fatigue and other signs of psychasthenia were found to be the major health effects associated with increased thallium levels in urine and hair (Peter and Viraraghavan 2005).

2.2.14 Tin

Tin (Sn) is one of the metals of antiquity and its use with copper in the alloy bronze contributed to a major development in human history since the Bronze Age (Alloway 2013).

The distribution of Sn in the Earth's crust averages at 2.5 mg kg^{-1} crustal abundance with two oxidation states (II and IV), of which Sn^{IV} is prevalent in both inorganic and organic compounds; yet, it is a component of few minerals, of which only cassiterite (SnO_2) is commercially important (Adriano 2001). Organometallic complexes with Sn are prevalent in aquatic systems (see this volume, Chap. 2), and contribute to its enrichment in biolites (Alloway 2013).

Malaysia is the main Sn producer in the world, with about 50 % of the total Sn produced. Major uses of Sn are in alloys with Zn and Cd (tinplate and bronze), in vehicle and aerospace industry, and as protective coating agent; organic complexes (e.g. tributyltin, TBT) are used mostly as biocides in agriculture and as antifouling agent in paints, with significant environmental effects (Adriano 2001). Organotins are more ubiquitous sources of Sn in the environment than inorganic forms, and are added to soil by atmospheric dust deposition, fungicidal sprays and sewage sludge spread on agricultural land, constituting the greatest ecotoxicity hazard.

In uncontaminated soils, Sn is largely derived from its content in the bedrocks, and occurs with a range between 1 and 10 mg kg^{-1}. In polluted sites, however, its concentration may be highly elevated, as near smelter areas, where it may achieve up to 1,000 mg kg^{-1} (Kabata-Pendias and Mukherjee 2007). Significant differences in Sn concentrations in soils among various countries have been recorded (0.89 mg kg^{-1} in USA; 2 mg kg^{-1} in andisols of Japan; 1.8 mg kg^{-1} in Swedish topsoils, with a range 0.4–8.6 mg kg^{-1}; 3 mg kg^{-1} in tea soils of Nyasaland (Adriano 2001; Kabata-Pendias and Mukherjee 2007, and references therein).

Tin is fairly immobile in typical arable soils, and is considered a non essential element in plant nutrition; conversely, it is considered as toxic to both higher plants

and fungi. Hence, plants tend to accumulate tin in roots when it occurs in easily available forms in soils, and it is poorly translocated to shoots and leaves. Yet, as reported by Tyler (2005), the biological absorption coefficient (BAC = metal in root /metal in soil) for tin is about 0.10. Common ranges of Sn in food plants and cereal grains are reported to be between 0.01 and 0.12 mg kg^{-1} (Kabata-Pendias and Pendias 2001). Conversely, plants growing in mineralized or contaminated soils accumulate Sn to high levels (up to 2,000 mg kg^{-1} in vegetation near Sn-smelters) (Kabata-Pendias and Mukherjee 2007).

The organic tin compounds (OTCs), and particularly TBT, are regarded as contaminants in the environment, with particular reference to the aquatic systems. High contamination of ports and marinas waters has been reported, and TBT residues have been recorded in fish and marine mammals living in contaminated waters, with TBT concentrations up to 2,000 ng g^{-1} in dolphin liver in the Mediterranean sea (Adriano 2001). Given the recognized toxicological importance of OTCs to aquatic biota, the recent detection of TBT in human blood points to its potential effect on human health. Indeed, as stated by Alloway (2013), OTCs behave as enzyme disruptors in many animal species and there is concern about their possible impact on human health.

Recent findings indicate that Sn is likely to be an essential trace element (micronutrient) for mammals, with low mammalian toxicity (Alloway 2013 and references therein). It is reported that mammalian tissues contain Sn in the range 0.1–0.85 mg kg^{-1}, with liver and kidney being the target organs (Kabata-Pendias and Mukherjee 2007). Tin in the inorganic forms is considered as being relatively non-toxic because of their low solubility, whereas some OTCs are considered to be toxic, although information on OTC contents to in human tissues is quite rare.

Human exposure pathways to Sn are mainly from seafood ingestion, with an exception of industrial areas where its concentrations in water and air are elevated; inhalation, and dermal adsorption are minor pathways. Therefore, there is considerable concern about the risk to people consuming a large amount of seafood due to the accumulation of tributyltin (TBT) in marine ecosystems, where up to 78 μg kg^{-1}OTCs in tissues of people from Japan have been reported (Kabata-Pendias and Mukherjee 2007). Mammalian toxicity of OTCs is likely due to their lipophilic character that enables them to penetrate and damage cell membranes, mitochondria, and DNA (Alloway 2013 and references therein).

The typical dietary intake of total Sn in humans is 1–40 mg day^{-1} (Alloway 2013), and the free-hazard inorganic Sn intake has been proposed not to overcome 2 mg kg^{-1} body weight. Canned foods, especially fruits and vegetable products, are considered to be the main source of Sn in the diet. Some canned fruits and juice may contain Sn at the range from 141 to 2,000 mg kg^{-1} (Kabata-Pendias and Mukherjee 2007; Alloway 2013). Higher levels of Sn may be found in some processed food due to the addition of Sn-based preservatives and stabilizers such as stannous chloride (Kabata-Pendias and Mukherjee 2007).

Increased Sn concentration in food may cause acute gastric irritation, impaired reproductivity, and bone strength failure. It is also considered to be genotoxic. Some organotins are highly dermal irritants (Kabata-Pendias and Mukherjee 2007).

As in the case of other elements (e.g. Mo, Se), a dietary deficiency of Sn is likely to induce some disturbances in humans, as hair loss, depressed growth, response to sound, feed efficiency, synergic decrease of other elements in various organs (e.g. Fe in kidney, muscle and spleen) (Alloway 2013).

2.2.15 Tungsten

Tungsten (W) is an emerging PHE about which there is little information, although it is an important strategic element with a wide range of applications in modern science and technology (e.g. metallurgy, lamp filaments and x-ray tubes), and military applications as substitute for the toxic Pb in ammunition (Alloway 2013 and references therein).

It occurs naturally in small concentrations (1–2 mg kg^{-1}) in granitic and sedimentary rocks, while in soils it ranges from 0.5 (in USA) to 85 mg kg^{-1} (in China, that is the biggest utilizer), with even 100–200 mg kg^{-1} in the vicinity of ore-processing plants (Kabata-Pendias and Mukherjee 2007).

There are confusing reports on the phytoavailability of W, but plant uptake and accumulation of W is apparently related to the soil content (Alloway 2013). The common range of W in terrestrial plants is generally very low, being established at the range of <1–150 μg kg^{-1}, with concentrations in mosses up to 2,500 μg kg^{-1} (Reimann and de Caritat 1998).

There is some evidence that W, similarly to Mo, might have a biological function in plants, since the behaviour of Mo and W is similar in biochemical processes (Alloway 2013). However, W displays competitive inhibition of Mo, reducing the enzyme catalytic activity. Moreover, some observations on the antagonistic interactions between W and Mo have been recorded, and some substitution by W for Mo has been reported (Kabata-Pendias and Pendias 2001).

The biological functions of tungsten are not well known. Information on adverse and stimulating effects of W in animals and humans are confusing and need more studies. The only available (and contradictory) data for human fluids indicate concentrations of W as follows: 1–390 ng L^{-1} in blood, and 5–320 ng L^{-1}in urine. The reference value for W in urine has been estimated as 860 ng L^{-1}, and the intake of W by individual animals is estimated as 13 μg day^{-1} (Kabata-Pendias and Mukherjee 2007).

It appears that the toxicity of W depends on the solubility of its compounds, and is the highest for polytungstates. Easily soluble W (e.g., from sodium tungstate, Na_2WO_4) is also easily absorbed and is harmful to the nervous system. Dust inhalation is a major exposure pathway for tool-manufacturing workers. The reference value for W in atmospheric dust in Germany has been set at 1 mg m^{-3} for soluble W compounds (Kabata-Pendias and Mukherjee 2007).

The potential environmental effects of W are essentially unknown and not yet thoroughly investigated, but adverse toxicological effects of W (e.g. growth enhancement and moderate toxicity to certain plants and animal species associated with the presence of W) have been recorded recently (Alloway 2013). Fibrotic lung

changes are observed in animals under exposure to tungsten-carbide dust (Kabata-Pendias and Mukherjee 2007). Therefore, its designation as a non-toxic and environmentally friendly metal should be reconsidered.

2.2.16 Vanadium

Vanadium is a polyvalent element, with various oxidation states and a tendency to form oxyanions, a property it shares with Mo, As, W, and P (Adriano 2001). It is ubiquitous in the lithosphere, with some prevalence in igneous rocks (135 mg kg^{-1} on average) and shale (130 mg kg^{-1}), and is widely distributed in nature. Vanadium is largely used in manufacturing steel (80 %), in ceramics, in some alloys with Sn, in chemical industry. Vanadium is the major trace metal in petroleum products. Combustion of coals and oils represents the major source of environmental V enrichment. Industrial activities and anthropogenic emissions have increased significantly V concentrations in soils: the world median is 90 mg kg^{-1}; the range 3–500 mg kg^{-1} (Reimann and de Caritat 1998). Therefore, its potential to enter the food chain is significant, and the number of people exposed to V pollution is increasing (Alloway 2013).

Vanadium is not considered to be an essential element for higher plants; however, some evidence exists that it may be essential to bacteria, fungi and algae as *Azotobacter*, *Aspergillus* and *Scenedesmus* (Adriano 2001). Its content in plants vary broadly: from 10 to 700 mg kg^{-1} (Kabata-Pendias and Mukherjee 2007). Trace concentrations of V have been reported to benefit plant growth, while higher concentrations are toxic (Alloway 2013). Adriano (2001) reports a mean V content of 1 mg kg^{-1} in plants growing on not contaminated soils, with roots having more V than the aerial tissues; no significant correlation was observed between V in soils and in plants, and it is concluded that soils having high V contents should not pose any risk for V bioaccumulation in the food chain.

Vanadium toxicity has proven virtually not existent for plants; however, excess V seems to interfere with chlorophyll synthesis, photosynthetic electron transport, inhibit the plasma membrane ATPase and acid phosphatase (Adriano 2001). Elevated V content in plants is of a great significance since V^{5+} is recognized as a potent inhibitor of several enzymes (Kabata-Pendias and Mukherjee 2007).

Conversely, V is an essential element for some marine organisms, and has long been suspected to have a biological function in humans and domestic animals as well (Steinnes 2009); this explains the increasing interest for V content in plant material.

The critical level of V for livestock has been established at 25 mg kg^{-1} of total diet; if it would be exceeded, the environmental concern about V is primarily due to the air pollution aspect (Adriano 2001; see also this volume, Chap. 1). Although information on the environmental biogeochemistry of V is nearly insignificant, and little is known on the toxicological effects of V in aquatic systems, it is known to have low toxicity to fish (this volume, Chap. 2).

The common pathways of V exposure for the general population are ingestion of food, and dust inhalation during everyday activities; soils containing increased levels of V may result in their increased V exposure. Airborne V can cause irritation of eyes and respiratory track. The threshold level for V toxicity to humans is established at 10–20 mg day^{-1}; requirement is probably less than 2 mg day^{-1} (Alloway 2013).

In humans and animals, V appears to have insulin-like actions at the cellular level, stimulating cellular proliferation and differentiation. Lipids level in blood and abnormalities in bone mineralization have also been reported with V deficiency, suggesting it to play a role in the formation and function of bone and connective tissue (Alloway 2013). Vanadium is easily reduced to V(IV), leading to accumulation of ROS which induce lipid peroxidation, oxidative DNA damage and apoptosis (Franco et al. 2009). Highly oxidized species of V are toxic, especially to nervous system and digestion processes (Kabata-Pendias and Mukherjee 2007).

The USEPA has not listed V as a pollutant requiring urgent research and legislation, because *"there is no evidence that the general population is at risk, either through deficiency of, or overexposure to vanadium"* (USEPA 1991).

2.2.17 Zinc

Among trace elements, zinc is a micronutrient for all biota, and is one of the most important contributors to human health, being essential for the functioning of a great number of enzymes. It is an important component of the earth's crust (24th element in the ranking of abundance), where it is present in rocks and soils in amounts ranging from 40 mg kg^{-1} in acid rocks (granite and gneiss) to 110 mg kg^{-1} in basalts. The average content of soils worldwide is 55 mg kg^{-1}, with typical background concentrations 10–300 mg Zn kg^{-1} (Kabata-Pendias and Mukherjee 2007). Significant differences, up to hundreds of mg Zn kg^{-1} can be recorded at several sites, reflecting the high Zn soil parent material, the presence of mining areas and the anthropic contribution (sewage sludge application, fertilizers, atmospheric emissions from industries and smelters). Yet, besides the limited metal utilization by Romans, and until last century, Zn occurred naturally in soils with the above reported range, and it was only from the middle of nineteenth century that Zn production started to increase dramatically, and has been almost doubled in the last 20 years. The main utilization (50 %) of Zn produced worldwide (11×10^6 tons) is in the galvanic industry, followed by Zn alloys, tyres and rubber (Alloway 2013).

The increased Zn production has released consistent industrial Zn emissions in the atmosphere, and the subsequent deposition onto soil and water determined environmental contamination, with possible ecotoxicological effects. Yet, elevated Zn concentrations can cause toxic effects to plants, soil organisms and microorganisms, and to wildlife, and these ecotoxicological effects precede possible effects on humans. Therefore, risk assessment on Zn should be focuses on the effects to soil biota and soil functioning, before considering human risk.

Zinc in waters is not very toxic to the biota, however, concentrations above 240 μg l^{-1} may have adverse effects on some sensitive organisms, as for example salmons (Kabata-Pendias and Mukherjee 2007 and references therein).

Zinc has essential functions in the metabolism of carbohydrates, proteins, and phosphate in plants; moreover, it is an active component of a variety of enzymes and also influences the permeability of membranes and stabilizes cellular components (Kabata-Pendias and Mukherjee 2007). Therefore, plant response to Zn content, as well as several other trace elements (e.g. Cu, Mo, Se), relies to both excess and deficient Zn levels.

Zinc toxicity and Zn tolerance in plants have been of concern because of the prolonged use of Zn fertilizers, the application of sewage sludge, and other pollution sources, that enhances Zn content of surface soils. Although Zn content of plants vary considerably, Zn uptake and translocation from soil to the aerial parts seems to be effectively limited by a barrier root. Notwithstanding, phytotoxicity is reported relatively often, although no apparent signs of toxicity are present. Typical Zn concentrations in healthy plants are 60 mg Zn kg^{-1}, although an yield reduction is likely to occur at 100–500 mg Zn kg^{-1} (Alloway 2013). The toxicity limit for Zn depends on the plants species and genotypes, as well as on the growth stage. Kabata-Pendias and Mukherjee (2007) report that sensitive terrestrial plants die when soil Zn concentration exceeds 100 mg kg^{-1}, and photosynthesis is stopped when the content is more than 178 mg Zn kg^{-1}. Conversely, some species (e.g. *Thlaspi caerulescens*) are known to hyperaccumulate Zn above 10,000 mg kg^{-1}, without showing any toxic symptoms (McGrath 1995).

The opposite concern is the Zn deficiency in soils and, accordingly, in plants, which is a worldwide problem and is reflected also on human health. Approximately one third of land all over the world, most of which in developing countries (central Africa, middle and far East, southern America), is Zn-deficient. Zinc deficient soils produce food crops that are low in Zn (e.g. below 15 mg kg^{-1} in wheat grains), and consequently Zn deficiency may affect human population residing in that areas and consuming deficient food; consistently, it has been estimated that approximately 1/3 of the world population may be affected. Zinc deficiency in plants is generally observed when the plant contains less than 20 mg kg^{-1} of this metal. As previously stated, Zn is not readily translocated from roots to the aerial parts of plant; generally, deficiency occurs firstly in younger leaves. Deficiency symptoms are plant shortness and underdevelopment as the result of an inadequate supply of the growth hormone (Kabata-Pendias and Mukherjee (2007); large yield losses, due to Zn deficiency, have been reported for various crops in USA and Australia.

Zinc is actually essential for mammals, and must be supplied continuously with the diet; indeed, the main pathway of Zn intake is by food ingestion. The required amounts of Zn vary highly (10–200 mg kg^{-1}), and are generally achieved with normal feeding; few cases of Zn deficiency have been reported. Symptoms of Zn deficiency, such as decreased growth, testicular atrophy, alopecia, and dermal lesions have been observed mainly in young animals, as reported by Kabata-Pendias and Mukherjee (2007).

Farm animals are rather tolerant to high Zn levels in the diet. Horses are the most sensitive to the Zn excess, with symptoms as lameness, osteoporosis, and lymphoid hyperplasia; lethal dose is 10 mg Zn kg^{-1} body weight.

Zinc plays a fundamental role in human health, and is regarded as second only to iron in importance; it is a structural component of several enzymes, and participates in the genetic expression as well. It is important during pregnancy, for brain growth in infants, and in immunocompetence (Steinnes 2009). Deficiency of Zn in the human diet was suspected first in 1961 in some Iranian males with a syndrome that includes hypogonadism, dwarfism, hepatosplenomegaly, geophagia and anaemia (Oliver 1997). Other symptoms include skin lesions, increased susceptibility to infections, growth retardation, delayed sexual and skeletal maturation, anorexia, and behavioral effects. Moderate Zn deficiency has been cited as a major aetiological factor in the adolescent nutritional dwarfism syndrome in the Middle East. Yet, in many Central Asian and Middle Eastern countries wheat provides 50 % of the daily energy intake, and the proportion can exceed 70 % in rural areas. A daily portion of 400 g rice for subsistence farmers contributes less than 10 mg Zn day^{-1}, an amount that counteracts a daily consumption of 250 g meat and 500 g dairy products that contributes >20 mg Zn in normal diet (Alloway 2013).

Opposite to deficiency, zinc can also accumulate in human diets to the point of toxicity. Its intake from food varies highly and depends on several factors, but often on interactions with other metals. Important antagonistic relationship is between Zn-Cd and Zn-Cu. Also increased levels of Ca and Mg in food inhibit its availability (Kabata-Pendias and Pendias 2001). The safe recommended intake of Zn is 15 μg day^{-1}(Oliver 1997), while the average content in tissues of the reference man (40–60 years, 70 kg body weight) is 33 mg kg^{-1}. The ingestion or inhalation of larger doses of Zn, especially in forms of inorganic compounds, can be harmful to individuals. It can damage alimentary tracts, and affect diarrhoea and fever (Kabata-Pendias and Mukherjee 2007); the lethal dose for humans is expected to be less than 3 g kg^{-1} body weight.

3 Conclusions

The flux of elements from the soil/plant system to humans through the food chain is rather well known since the early research papers of the last century (see Oliver 1997 and references therein). The effects of most trace metals on human health seem to be less well understood, partly because of the interactions between them, and partly because of the complex metabolic reactions in the human body, although there are several well-documented case studies.

Despite the copious research addressed to this topic, with thousands of papers published in the last decades, there is still a paucity of quantitative information on the relations between elements in soils and human health. Much is known about the functions of most elements in human body, but there is increasing evidence that the interactions among them are more complex than originally thought. Uncertainty is

still prevailing, particularly with non essential elements that are "suspected" to be harmful to humans. The non essential elements As, Cd, Hg, Pb have attracted most attention worldwide, due to their toxicity towards living organisms (Adriano 2001). Other elements (Al, Be, Bi, Sb, Sn, Tl, V, W) are likely harmful, but may play some beneficial functions not yet well known, and should be more investigated.

Among essential elements, Cu, Fe and Zn are of considerable interest. Iron and zinc deficiencies in humans are rather common, and their effects already known. Other essential elements (B, Co, Cr, F, I, Mn, Mo, Ni, Se) have received less attention.

Potentially (and actually) harmful elements are responsible for some of the main threats to human health. Arsenic is a silent killer, that takes 8–14 years to develop arsenicosis, an As-poisoning that affects more than 20 millions people exposed to As through drinking water (Adriano 2001). Skin pigmentation, diarrhoea, and ulcers are the effects appearing during the initial stage. In the most severe cases, arsenicosis causes liver and renal deficiencies or cancer that may lead to death. Dozen of death induced by skin cancer have been reported in recent years.

Cadmium toxicity is considered among the worst human diseases. Epidemiological studies indicate that renal dysfunctions are caused by Cd poisoning, followed by development of osteomalacia. Once in the body, the elimination of Cd is very slow, with a biological half-life of 20 year. The kidney is considered as the critical target organ for Cd-induced cancer in the general population.

Inorganic Hg is effectively absorbed via the lungs, passing through the blood-brain barrier, and subsequently bioaccumulating in the brain, provoking the Minamata disease (mercurialism). Hg is distributed to all tissues within a short time (ca 4 days), its toxic effects are selective to the nervous system (central system and peripheral nerves). Hg bioaccumulates and biomagnifies in the aquatic food chain, that constitutes the predominant pathway of human exposure to Hg.

Lead enters the human body mainly via inhalation and ingestion. The pronounced toxic effects of Pb (plumbism) are manifested as dysfunction in the nervous system. The neurological effects on children of the slow (chronic) accumulation of Pb should be a matter of immediate concern: US EPA recommends that all children up to 6 year of age be screened for Pb at least once yearly. In short, Pb is the greatest cause of global public health concern.

Deficiency in the soil is implicated in selenium disease (selenosis). Shortage of Se in China soils induce Keshan disease. Evidently soils are deficient in Se, as well as the general population diet. Selenium deficiency is also considered to be implicated in the incidence of cancer and heart disease.

Potential toxicity in humans from chronic exposure to Tl, Sn, V, and Sb has also been reported. Also, there is a current question nowadays: does free Al in poor acid soil contribute to Alzheimer's disease? Yes, it does! and soil acidification is a current process today.

As Oliver pointed out (Oliver 1997), "if people were able to optimize their intake of trace elements, then their health might benefit in the same way as it has done through the controlling of infectious diseases during this century". On this roadmap, epidemiological research is providing increasing evidences that cancer is largely a

man-made disorder and that it should be susceptible to preventive intervention. The causes appear to be connected largely with our life-style, that is, smoking and eating habits, rather than with specific industrial factors. The major actions are:

- excessive tobacco usage continues to be the principal challenge in the area of lung cancer prevention;
- heavy alcohol intake enhances the risk of upper alimentary and upper respiratory tract cancer among smokers;
- the greater Mn content in soils, the smaller cancer incidence;
- the cancer incidence is raised by a high Zn/Cu ratio;
- The tissue-damaging activity of the rheumatoid arthritis is accelerated by deficient intake of copper, zinc and/or selenium;
- a deficiency of Mn and Se, as well as an abundance of Zn, has a carcinogenic effect?

In conclusion, the role of geochemical factors in the aetiology of human diseases should be deepened, in combination with epidemiologists, soil scientists, social statisticians and other specialists. It has been observed since the 1980s (Lag 1980, 1984, 1987) that there are considerable geographical variations in the distribution of human diseases, and these variations depend on metal distribution, which, in turn, depends on several factors: geology, soils, climate, etc. Arsenicosis is diffused mainly in the Indian region, diabetes and cardiac infarctions are not found among Eskimoes, as well as the rare occurrence of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and psoriasis, and the cancer pattern is quite different from the EU one. Most diseases (cardiac-infarction, rheumatoid arthritis, multiple sclerosis, psoriasis) in Nordic Baltic are under the influence of Se-supply. People inhabiting coastal areas proved to have higher dietary intake of aquatic foodstuff, to which correspond higher Hg levels in blood and hair.

Epidemiological studies have not revealed any single factor that could account for differences in breast cancer incidence. Rather, a combination of factors (environmental, genetic, behavioral etc.) is likely the triggering cause for the onset of cancer.

Anomalous situations (geochemical hotspots) may occur in the vicinity of mining areas or close to industrial activities, where the metal burden of humans may be augmented through foodstuffs ingestion, drinking water, dust and air inhalation.

If the soil, or food crop, is not contaminated, human exposure through food consumption is substantially below the provisional tolerable intake guideline for the FAO/WHO (WHO 1996), and this is what people should achieve for a sustainable environmental and human life quality.

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Author Queries

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