32 Trophic Transfer of Trace Elements and Associated Human Health Effects

Amit Love and C.R. Babu

CONTENTS

32.1 INTRODUCTION

Trace elements (metals and metalloids) are ubiquitous in their presence in water, air, and soil. These elements are introduced into the environment by natural and anthropogenic processes [1]. It has been shown that anthropogenic processes have become the most important factor in the global biogeochemical cycling of some trace elements [2]. Anthropogenic activities such as mining, metal smelting, incineration and disposal of wastes, and combustion of fossil fuels have greatly influenced the mobilization of these elements in the biosphere [3]. Elevated concentrations of different elements in environmental resources such as water, air, and soil are of great concern because these elements are infinitely persistent and immutable in nature [4]. Persistence of trace elements lends them the

potential to bioaccumulate in living organisms — directly, through exposure to contaminated water, air, and soil, and indirectly, by trophic transfer through the food chain.

Society is concerned for the increased accumulation of these elements in biota because of the imminent probability of humans being exposed to these elements through trophic transfer (exposure via food chains) [5]. Trophic transfer of trace elements to humans is an exposure pathway generally characterized by chronic, sublethal exposure to trace elements, which can result in the manifestations of various disease states. It is acknowledged that growth, health, fertility, and well-being of humans is influenced by the amount and proportion of various trace elements from food and environment to which they are exposed [6]. Trace elements such as Cd, Cr, and As have adverse health effects and are known carcinogens and mutagens in humans [7–9]; additionally, some trace elements are also involved in generation of reactive oxygen species [10] that have been implicated in many human diseases. This chapter elucidates and outlines current understanding of the process of bioaccumulation and trophic transfer of trace elements in biota, and the associated human health effects.

32.2 BIOACCUMULATION AND TROPHIC TRANSFER OF TRACE ELEMENTS

Living organisms bioaccumulate trace elements due to direct exposure to contaminated water, air, and soil or indirectly through contaminated food. The relative contribution of each of these sources to the total body burden of the organism varies depending upon the specific environmental conditions, the organism, and the interaction between them. It is possible that, in a particular environmental setting, direct exposure due to contaminated water, air, and soil individually or collectively may contribute more to the trace element burden of a living organism than exposure through food or vice versa. For example, the potential human health risk associated with inorganic arsenic exposure is predominantly due to intake of As-contaminated water; however, in the case of methyl mercury exposure, health risk is associated with the consumption of contaminated food like fish and shell fish [11,12].

Bioaccumulation of trace elements in receptor biota and humans through food is essentially related to trophic transfer of trace elements in terrestrial and aquatic ecosystems. Increasingly, sophisticated analytical methods such as stable isotope analysis are being used to resolve food chain structure and define trophic position of biota in the food web [13,14]. Trophic transfer of trace elements within the food web has been demonstrated by relating the metal levels in the dietary components with those assimilated by animals [15]; indices such as bioaccumulation, bioconcentration, and biomagnification factors have been routinely used to estimate trophic transfer in the food chains [16].

Exposure resulting from terrestrial and aquatic food chains to humans and biota must be analyzed separately due to the fundamental differences between them. The number of trophic levels in the terrestrial food chain is greatly reduced compared to the aquatic food chain. Moreover, the terrestrial herbivores demonstrate low efficiency of converting plant biomass into protein due to a large percentage of indigestible structural material containing high levels of cellulose and lignin in terrestrial plants. However, the low energy efficiency causes higher consumption rates of food stuffs in herbivores, which can effectively intensify metal uptake in food webs within contaminated areas [17].

This chapter focuses on trophic transfer of trace elements as an exposure pathway for biota and humans. Trophic transfer of trace elements chronically exposes humans to sublethal concentration of elements, which can build overtime to reach toxic levels. The most important trace elements in terms of their trophic transfer potential through the food chain are Cd, Hg, Pb, As, and Se [8]. Trophic transfer of trace elements and their bioaccumulation in biota have associated ecological and human health effects.

TABLE 32.1
Trace Element Content in a Typical International Diet

Meal	As (μg)	Cd (μg)	Hg (μg)	Pb (μg)
Breakfast				
Milk (200 ml)		2		0.7
Fruits (200 g)		0.2		1.6
Cereals (100g)				3.2
Lunch				
Spinach (100 g)		6		3.1
Broccoli (50 g)		0.5		1.6
Tomatoes (50 g)		0.7		1.6
Egg (80 g)		0.8		1.6
Fish (100 g)	100	1.5	0.6	
Water (300 ml)	3	0.03		0.6
Dinner				
Meat (200 g)		2		6.3
Carrots (50 g)		0.9		
Cauliflower (50 g)		0.5		
Rice (80 g)		0.4		1.3
Potato (100 g)		2		1.3
Wine (125 ml)	2.5			0.6
Total	105.5	17.53	0.6	23.5

Source: Adapted from Rojas, E., Herrera, L.A. et al., *Mut. Res*., 443, 157, 1999.

Humans are necessarily exposed to trace elements through the consumption of contaminated food items in the absence of any specific environmental and occupational exposure. An average human diet includes an assortment of products derived from plants and animals that would include food items like fruits, vegetables, grains and cereals, milk, eggs, meat, and fish (Table 32.1).

As is evident, these items are sourced from different plant and animal species. Predominantly, all the plant products are derived form terrestrial agricultural food chains; while animal products may come from terrestrial or aquatic animal species. To estimate human exposure due to trophic transfer of trace elements and how it relates to human health reasonably, it is imperative to understand the processes associated with the trace element content in different tissues of plant and animal species.

32.2.1 Terrestrial Ecosystems

Trace elements enter the terrestrial food chains predominantly through plants that mobilize these elements from contaminated soils. It is necessary to differentiate the various steps through which a trace element passes as it progresses from soil through the food chain to the human receptor. As trace elements are transferred from the soil to the plant and then further to primary and secondary consumers, different processes influence the amount of trace element available at each trophic level and what will eventually reach the human endpoint [5]. Exposure of different animal species and humans to trace elements due to consumption of plant products is influenced not only by the trace element content in the consumed plant part, but also by the plant-mediated changes in trace element speciation that may alter the rate and extent of gastrointestinal absorption after ingestion of plant tissue by animals [18]. Furthermore, trophic transfer and bioaccumulation of trace elements by animals is influenced by different ecological host factors [19]. In terrestrial ecosystems, trophic transfer of trace elements has two distinct components keeping in view humans as the ultimate

receptor: bioaccumulation of trace elements by the plants that mobilize these elements into the food chain and trophic transfer and bioaccumulation in animals.

32.2.1.1 Bioaccumulation of Trace Elements in Plants

32.2.1.1.1 Bioavailability and Uptake of Trace Elements

Plants represent an important pathway for the movement of potentially toxic trace elements from contaminated soils to humans [18]. Elevated levels of trace elements in soil may lead to their uptake by plants, but, generally, a direct relationship between the total trace element content of soil and trace element content in different tissues of plants has not been conclusively established [20,21]. The trace elements in soils are associated with different chemical fractions of the soil, which affect their solubility and have a direct bearing on their mobility, bioavailability, and plant tissue levels [22]. The upper limit of trace element availability to plants depends upon the composition of the soil solution because root uptake requires the presence of soluble chemical species [23,24].

Plants' uptake of trace elements from the soil is influenced by physicochemical characteristics of the rhizosphere, the rhizosphere processes, and the chemical form of the trace element in the soil [22,25]. Plant roots and their associated microorganisms are known to modify the composition of soil, resulting in altered chemical mobility in the soil and acquisition of trace elements by the roots [26]. Rhizosphere soil may differ considerably from bulk soil with respect to modified pH, Eh, and concentration gradients of many minerals and organic ligands. The possible consequences of such changes on speciation of trace elements could explain to some extent the species-specific differences in soil to plant transfer factors [27].

The rhizosphere processes influence the rates of solubilization and the equilibrium concentration of individual ions associated with the soil solution, subsequently affecting the availability of essential and contaminant ions for absorption by the plants [23]. One of the hypotheses to explain the large uptake of certain trace metals by hyperaccumulators is that they solubilize the target metal in their rhizosphere [28–31].

Soil microorganisms affect trace element mobility and availability to plants by production of metal chelators, siderophores, alteration of soil pH, and solubilization of metal phosphates; they also influence root parameters such as root morphology, growth, and root exudation, leading to increased uptake trace metals [32]. Abou-Shanab et al. [32] showed that rhizobacteria play an important role in increasing the Ni availability in soil by releasing Ni from the nonlabile phase in the soil, thus enhancing the availability to the plants. In contrast, vesicular–arbuscular fungi in the roots of the plants reduced the uptake of trace elements, leading to increased plant biomass due to decreased uptake of heavy metals [33–35]. Furthermore, Leyval and Joner [36] also concluded that ecto- and AM-mycorrhizae tended to reduce metal concentration in the shoots of nonhyperaccumulator plants. Certain plant growth-promoting bacteria also reduce the metal stress on plants. Burd et al. [37] found that *Kluyvera ascorbata* SUD 165, a plant growth-promoting bacteria, decreased toxicity of Ni to seedlings by lowering the level of stress ethylene induced by Ni in canola, rather than by reducing uptake by seedling.

Soils are often contaminated with more than one trace element. These trace elements interact in various ways to increase or decrease the uptake and transfer of each other from the soil to plants. Podar et al. [38] showed that the relative uptake of cadmium in the presence of zinc is reduced by the plants, suggesting that human health risk from consuming parts of plants grown on Cd-contaminated soils is relatively low when Zn is also present. In addition to the variation in the bioavailability of different elements in the soils, the uptake and translocation characteristics of metals vary between different plant species, and even between population and cultivars [39]. Baker [40] found that plant species differed considerably in their metal uptake characteristics and that, for any given species, uptake may vary between different metals. For example, the genus *Salix* is known for its high uptake of Cd [41]. A study of native plants in the forest ecosystem of Norway

indicated that interspecific differences in the uptake were more evident for nonessential elements like Cd and Pb, compared to essential ones such as Zn and Cu [42].

32.2.1.1.2 Partitioning of Trace Elements in Different Plant Tissues

Plants partition the trace elements into different tissues based upon the physiological mechanisms of the plant species and also the trace metal elements under consideration. Shoot metal content is determined by root uptake and sequestration within root vacuoles, translocation in the xylem and phloem, and dilution within the shoot through growth [43]. Nan et al. [44] studied the transfer of Cd and Zn from calcareous soils near a nonferrous mining and smelting bases to spring wheat (*Triticum aestivum*) and corn (*Zea mays*) tissues under field conditions. They found that Zn and Cd were present in highest concentrations in the roots; the lowest concentration was found in the seeds. This pattern of tissue distribution of trace elements suggests the presence of a physiological mechanism that prevents the excessive movements of Zn and Cd in the edible parts of the plants.

Torres and Johnson [15] found that roots of *Scirpus robustus* had elevated concentration of Pb and Ni compared to seeds, which was consistent with pattern of bioaccumulation in plants. Lubben and Sauerbeck [45] also found that seeds had lower trace element content compared to the other plant parts. Generally, nonessential trace elements become immobilized in the roots and undergo limited translocation to the above-ground structures such as leaves and seeds. Root-to-shoot transfer may not be constant for a given species; soil factors and probably also the age of the plant play an equally significant role [27].

Broadley et al. [43] found that plant species of families Chenopodiaceae, Polygonaceae, and Amaranthaceae belonging to order Caryophyllales have the general ability to accumulate trace elements in their shoots. On the other hand, crop plants such as cereals and alliums have low concentrations of shoot metal. It seems that certain plant groups have evolved their own spectrum of ecological and physiological adaptations. For instance, grasses have developed effective regulatory mechanisms at root level. In grass shoots, the element content, even on ore soils, tends to be much lower than broad-leaved herbs.

On the other hand, some plants termed as hyperaccumulators have extreme adaptation to accumulate high concentration of trace elements in their shoots. Brooks et al. [46] introduced the term "hyperaccumulator" to describe plants capable of accumulating more than 1000 μg of Ni/g on a dry leaf weight basis in their natural habitats. The same criteria were also applied to elements such as Co, Cu, and Pb; whereas for Cd and Zn, the respective thresholds are 100 and 10,000 μg/g dry leaves [47,48]. Metal hyperaccumulation is a rare phenomenon in terrestrial higher plants. To date about 400 plant species have been identified as metal hyperaccumulators, representing <0.2% of all angiosperms [47,48].

Generally, non-hyperaccumulator plants have higher metal concentration in roots than in shoots [49,50]. The differential expression of transport or metal chelating proteins may account for phylogenetic differences in shoot metal concentrations between angiosperm clades and also for association between subsets of metals independent of phylogeny [43]. This kind of information on differentiation in shoot element content based on phylogenetic differentiation may be useful in estimating transfer coefficients when experimental data are not available and in improving predictions relative to soil-to-plant metal transfer in general [43]. On a relative scale, species-specific differences exist with respect to the concentration of metals in the roots and shoots of different plant species. The adaptive strategy adopted by the plant species with respect to the distribution of trace elements in different tissues has a profound impact on the trophic transfer of trace elements in the terrestrial food chain.

32.2.1.1.3 Chemical Modification of Trace Elements in Plants

The chemical modification of inorganic ions by plants can significantly influence their bioavailability to consuming animals. The nature and extent of this influence depends upon the element, and plant transport and deposition processes. Therefore, prediction of metal transfer in food chains

must be partially based on an understanding of the processes governing chemical form and speciation in specific plant systems [18].

32.2.1.2 Bioaccumulation of Trace Elements in Animals and Trophic Transfer

Increasingly, animals are used as sentinels of human exposure and as bioindicators of environmental contamination [51,52]. Different groups of animals differ with respect to the magnitude and type of exposure to trace elements. Several workers have advocated the use of free ranging animals such as mammals and birds for various reasons [53–55]. Small mammals depend exclusively on the quality of food, water, and air in a particular habitat and locality; they are physiologically similar enough to show comparable biological and physiological effects as humans [56,57]. Depending upon the group considered, birds are conspicuous, may occur over a wide geographical range, and show adverse effects at low concentrations [58]. Moreover, these animals can also provide an indication of the threat to other animal species and ecosystem health of the area. In this discussion, the focus is on small mammals and birds to understand the factors that influence bioaccumulation, trophic transfer of trace elements, and tissue distribution of the assimilated trace elements. Bioaccumulation patterns of trace elements in birds and small mammals can be affected due to exposure differences, individual differences, and species differences [19].

32.2.1.2.1 Exposure Differences

Differences in the exposure of animals to trace elements arise due to differences in habitat; home range; temporal patterns of a species; behavioral pattern, particularly foraging behavior; food chain effects; and spatial distribution of animal populations. Because habitat characteristics affect the home range of animal species, it becomes an important factor in determining the amount of exposure to trace elements. Attuquayefio et al. [59] found that small mammals inhabiting unproductive ecosystems had significantly larger home ranges than those inhabiting productive and species-rich habitats. It is well known that heavy metal-contaminated habitats have low primary productivity, which could probably result in animals foraging in adjacent areas where contamination is low and the abundance of food is greater. The consequential dilution of trace metals intake can lead to lack of correlation between dietary metal intake and the body/tissue concentration.

Marinussen and Vanderzee [60] found that a reduction in the cadmium concentration of tissues occurs due to increase in the home range of the animals. Larison et al. [61] found that foraging behavior of ptarmigans inhabiting the Colorado Rocky Mountains significantly influenced Cd exposure rates of the birds. They found that ptarmigans fed predominantly on willow (*Salix* spp.), which had elevated levels of Cd during winters and spring. However, during summers when other food items such as *Trifolium* spp., *Bistorta bistorta*, and *Geum rossii* become available, ptarmigans switched over to less contaminated food items and, in the process, consumed far less Cd. This expansion of diet of ptarmigans reduced the overall Cd exposure of the animal during summer months.

Exposure to trace elements such as Cd and Pb in free ranging wildlife like small mammals and birds depends on the dietary preferences of the animal species. Metcheva et al. [62] estimated the metal content in tissues of six species of small mammals from different habitats and found that the heavy metal loading in small mammals is not only due to specific accumulation features of physiological origins or preferable bioaccumulation of elements in respective organs and tissues, but also due to ecological and food characteristics. Hunter and Johnson [63] analyzed the total body burden and tissue distribution of heavy metals in small mammals. They found that *Apodemus sylvaticus*, which fed on fruits and seeds of ground cover vegetation and canopy species, had the lowest metal burden due to minimal translocation of metals to the reproductive structures of plants parts. On the other hand, *Sorex araneus* fed predominantly on detritivorous soil invertebrates and had the highest concentration of heavy metals.

Cooke and Johnson [64] also found high Cd concentration in the liver of *S. araneus*, most which was probably related to the food chain position of shrews, which accumulate higher Cd levels from their insectivorous diets. Mertens et al. [65] found that elevated concentration of Cd and Zn were present in the tissues of small mammals inhabiting disposal facilities for dredged materials; elevated tissue concentration of trace elements was related to the amount of Cd and Zn present in dietary items of the animals. Trace element content in the tissue of shrews was the highest as compared to all other small mammals due to high bioavailability of elements in the insectivorous diets. Ma [66] found that concentration of Pb in different tissues of small mammals was also very much dependent upon the diet.

Temporal changes associated with seasonal differences in the trace element content of the vegetation of an area can significantly affect the metal loading of the consuming animal because the trace element content in forage or food items can increase or decrease according to the season and plant species. Hunter et al. [67] reported seasonal variation in the concentration of Pb in vegetation growing on contaminated sites; lowest Pb concentration in vegetation was present in summer due to rapid increase in plant biomass resulting in growth dilution. These seasonal fluctuations may have implications for interpretation of concentration of lead in animal tissues because the metal content in diet reduces in summer. This indicates that the summer season may represent lower dietary exposure conditions for consumers than those experienced at other times of the year.

The diets of adult and juvenile small mammals also differ; in the case of wood mice, juveniles eat less seed and animal food compared to adults [68]. Such a marked shift in diet can lead to differential exposure of different age classes in the same species. However, Erry et al. [69] found no statistically significant difference in the stomach content of juveniles and adults with respect to arsenic content, suggesting that the degree of arsenic contamination may be similar in a wide range of animal forage. They also suggested that dietary overlap between different species and age classes is more pronounced on contaminated than uncontaminated sites, perhaps because diversity of food is limited and leads to similar dietary intake.

Another confounding factor that can obscure many ecotoxicological model predictions is the ingestion of soil by small mammals. The relative proportion of soil in the diet of small mammals may be less [70], but it can contribute immensely to the total trace element exposure. Erry et al. [69] found that soil contributed approximately 15% of total arsenic exposure to the small mammals. Shore [71] found significant correlation between liver and kidney levels of Cd in field mice, common shrews, and short-tailed voles and the levels of metals in the soils. Sharma and Shupe [72] also found significant relationship between Cd levels in rock squirrel (*Spermophilus variegates*) livers and the soil concentration; however, the same pattern was not found for As and Pb.

Shift in dietary preferences due to change in habitat type also has a profound influence on the exposure of trace elements. Hunter et al. [67] found that voles fed primarily on leaves and seeds of trees in woodlands; however, in the absence of trees, the bank voles fed opportunistically on any available plant and animal material. This leaf- and invertebrate-based diet resulted in higher exposure for the animals due to high trace metal content in metallophyte forbs [40] growing on contaminated sites. Furthermore, to obtain the energy equivalent of the fruit- and seed-rich diet, voles consumed increased amounts of leaf and animal material (soil invertebrates), leading to increased exposure to trace elements [73].

Some animal species or families are more vulnerable not only because of their foraging behavior and habitat characteristics but also because of their characteristic breeding biology. Seals that leave the water to breed on the beaches near industrial regions are exposed to higher levels of contaminants than those present near more pristine beaches. Similarly, birds that nest near urban estuaries and bays are more exposed to trace elements than those nesting in remote places [19].

32.2.1.2.2 Individual and Species Differences

Individual differences in bioaccumulation of trace elements may be related to age, gender, size, weight, nutrition, and genetic factors [19]. The studies on age-related accumulation in animals have

more or less focused on non-essential trace elements because of efficient regulatory homeostatic mechanisms that exist for essential elements. Age-related bioaccumulation of trace elements in animals has largely been found in the case of Cd [61,69,74–77]. Hunter et al. [76] found significant correlation between total body weight and Cd in liver and kidney of common shrew, reflecting the effect of increasing age on accumulation of trace metals in tissues. Pedersen and Myklebust [78] suggested that age-dependent accumulation of Cd in willow ptarmigan liver and kidney reaches a threshold value in birds in the first year of life. However, in mammals like cervides, a linear age-dependent accumulation of Cd seems to exist [79]. Larison et al. [61] found that Cd in the body tissues of ptarmigan chicks was negligible compared to older birds, which accumulated substantial amount of Cd over time.

Milton et al. [80] did not find any age accumulation of Pb in the bone tissue of small mammals across all age groups from subadults to adults. They suggested that the absence of a clear trend of age accumulation of Pb in bones of small mammals was due to exposure of unweaned pups and young animals to high dietary lead (via milk) and the fact that maximum bone deposition rate of Pb occurs in young animals [81]. This led to a rapid increase in the concentration of Pb in bone tissue of young animals, but in the case of adults and subadults, reduction in the rate of skeletal development could have produced a steady state Pb concentration. Erry et al. [69] also found that concentration of As in the stomach contents and body tissues of *Apodemus sylvaticus* and C*lethrionomys glareolus* did not vary with age class.

Gender differences in the bioaccumulation potential of trace elements have been observed in small mammals and birds. These differences have been at least partly attributed to the difference between the behavior of male and female individuals of a species. Larison et al. [61] found differences in the wintering distribution of male and female ptarmigans. They found that female ptarmigans overwinter in areas heavily contaminated with Cd, resulting in greater exposure of female ptarmigans and leading to higher accumulation of Cd in females compared to males.

Erry et al. [69] observed significant variation in arsenic intake between sexes in bank voles in which stomach arsenic concentration was higher in females than in males. Arsenic residues in the liver and, to a lesser extent, in the kidney were also higher in females than in males. The gender difference between male and female bank voles could not be explained on the basis of dietary preferences of the male and female voles because male and female voles had similar diets. It was suggested that the difference could have arisen due to the larger home range of male voles, which might have led to the dilution of the metal content. The same argument could not be used to explain the absence of any difference with respect to trace element content of wood mice male and female individuals, even when males of the species have a larger home range. This shows that gender differences in trace element content are arising due to factors other than behavioral and need further investigation.

Species-specific differences with respect to retention and accumulation of nonessential trace elements in body tissues are determined by species dietary uptake as well as by physiological and behavioral characteristics [82]. Lock and Janssen [83] found that some species differences may relate to differences in internal toxicodynamics, leading to species differences even in closely related organisms. The risk of heavy metals accumulating to a toxic dose level in small mammals varies considerably between Rodentia and Insectivora from the same polluted area [77,84]. This could be due to differences in the diet and foraging behavior of the species of the two orders. Few studies have brought out the physiological basis of species-specific variation in mammalian species.

32.2.1.2.3 Tissue Distribution of Trace Elements

Distribution patterns of assimilated trace elements in tissues of animals highlight important differences between metabolically essential and non-essential elements [85]. Concentration of essential trace elements in animal tissues is effectively regulated through homeostatic mechanisms; these elements are widely distributed in different body tissues without restriction to any specific body organs or tissue. On the other hand, nonessential elements like Pb, As, and Cd have very specific

target organs where they preferentially accumulate [74–76,85,86]. Even though, essential trace element content in the body is generally regulated by the homeostatic mechanisms. These mechanisms may prove to be ineffective for animals exposed to very high concentrations of these elements, such as in cases in which animals inhabit highly polluted habitats [87].

Accumulation and distribution of trace metal elements in different body tissues are influenced by many factors, which include total heavy metal intake, Ca, phosphate and vitamin status in the diet, and metal–metal interaction [88,89]. Tissue accumulation of trace elements is also influenced by the presence of other competing elements. For example, Zn and Ca intake are known to influence the extent to which ingested Cd is absorbed and retained [90]. It may be noted that low Ca levels in the body can exacerbate Cd uptake [91]. Flick et al. [89] found that increased dietary Zn intake ameliorates the potential toxicity of administered Cd, presumably by competing with the latter element for specific enzymes and metabolic centers. Such competitive inhibition, which has been established mainly in lab studies, may have considerable significance in field studies because the two metals are naturally associated in the biosphere [92].

Hunter et al. [63].found that, regardless of the degree of environmental contamination, the retention of Cu in animal species was regulated by some kind of absorption–excretion equilibrium that adapts to maintain a homeostatic control. No retention control mechanism was evident in the case of Cd in small mammals whose distribution is characterized by preferential accumulation in the liver and kidney in mammals. Generally, trace elements concentrate in liver and kidney of animals; in contrast, the trace element content in the muscle tissue remains constant [74]. Kidney has greater affinity for Cd accumulation compared to liver in young animals and during low dietary exposure, although on a total organ basis, liver usually contains a greater percentage of the total body burden [76]. Age accumulation of Cd in renal tissue is a well established phenomenon and is associated with the formation of stable Cd–metallothionein complexes in liver and kidney [63,92,93]. On chronic exposure to high doses of Cd, kidneys become saturated with Cd and subsequent accumulation of Cd continues in the liver [76]. Erry et al. [69] found that arsenic concentrates preferentially in liver and kidney of mammals, but bone tissue bioaccumulates a maximum amount of Pb followed by kidney, liver, and muscle in small mammals [57,85].

Other workers have also found the same pattern of accumulation of lead [73,94]. Differential deposition of Pb in bone is because Pb mimics Ca during metabolism [57,95,96]. Bone tissue constitutes a physiologically important compartment into which Pb is absorbed, with a slow rate of equilibrium and half-life of over 10 years in humans [97]. In the animal body, one of the major repositories of lead other than bone tissue is kidney [80,86]. Even though liver is the first organ to encounter absorbed dietary lead distributed via bloodstream, Pb concentration in liver did not exceed 15 mg/kg even when kidney values in the same individual were as high as 60 mg/kg [98].

Seasonal variation in tissue concentration of trace elements has been reported for different organisms. Wlostowski et al. [99] found that low ambient temperature (+5°C) decreases the Cd accumulation in liver and kidney of bank voles compared to when voles were exposed to Cd at 20°C. They suggested that Cd intake may be affected through changes in Cu metabolism due to low temperature.

32.2.2 Aquatic Ecosystems

Exposure of humans to trace elements through the aquatic food chain is predominantly due to consumption of fish and aquatic invertebrates such as prawn and lobsters. Fish and aquatic invertebrates occupy different trophic levels depending upon their respective feeding ecology and foraging behavior. The bioaccumulation of trace elements varies greatly between different aquatic species and also between different trace elements. Some animal species, such as zooplanktons, accumulate high levels of metals, but others, such as fish, try to regulate the concentration of metals or sequester them with metallothioneins [100]. Due to the contrasting behavior and the fact that planktonic organisms and aquatic invertebrates form the base of many aquatic food chains, bioac-

cumulation patterns in aquatic invertebrates (including planktonic organisms) and fishes are dealt with separately.

32.2.2.1 Bioaccumulation in Planktonic Organisms and Aquatic Invertebrates

Planktonic organisms and aquatic invertebrates form the base of many aquatic food chains and thus have a crucial role in transfer of trace elements in the aquatic food web. It has been increasingly recognized that trophic transfer of trace elements in aquatic food chains is an important source for trace element accumulation in higher trophic-level organisms [101–103]. Trace element concentration in aquatic biota at any trophic level results from a combined effect of uptake from water and the diet; the uptake process is peculiar to each metal and taxa [104].

The uptake and bioaccumulation of trace elements in aquatic organisms is controlled by numerous geochemical, ecological, and physiological factors [105]. Aquatic invertebrates are exposed to trace elements from the particulate and the dissolved phases of water [106]. Trace elements dissolved in water are directly adsorbed onto the body surfaces, in contrast to trace elements present in the particulate phase, which are accumulated by animals following ingestion and digestion of food [106]. In copepods, trace elements accumulated from the dissolved phase are often associated with the exoskeleton of the organism [107]; consequently, they are less available to higher level consumers such as fish than trace elements, which are bioaccumulated in internal tissues of the organism [108].

Bioaccumulation of trace elements in aquatic invertebrates is strongly related to assimilation efficiency, particularly for trace elements accumulated from ingested food particles [107,109]. Trophic transfer of elements from zooplankton and other aquatic invertebrates to higher trophic levels is controlled by assimilation efficiency, efflux rate, and feeding and growth rates of the organism [110]. Elements with low assimilation efficiency in aquatic biota near the base of the food chain (zooplanktons) are unlikely to be transferred up the food chain. For example, in the case of methyl mercury, Mason et al. [111] suggested that its biomagnification in marine systems is mainly due to high assimilation by marine organisms.

All aquatic invertebrates accumulate trace metals in their tissues whether or not these are essential to metabolism. The difference in the accumulation pattern and intertaxon variability between aquatic invertebrates depends, among other things, upon the physiological mechanisms present in the organism with respect to trace metal elements. The physiological mechanisms for regulation of essential elements in different aquatic invertebrates vary from (1) regulation of body element concentration; (2) accumulation without excretion; and (3) accumulation with some excretion. For non-essential metals, the physiological mechanisms are (1) accumulation without excretion; and (2) accumulation with excretion [112].

Food chain transfer of trace elements and potential bioaccumulation at higher trophic levels is controlled by the quantity of element accumulated in the prey species at the lower trophic level as well as the form of detoxified storage of the accumulated element in the prey species [110,112]. Nott and Nicolaidou [113] have shown that the bioavailability to neogastropod mollusk predators of metals in detoxified metalliferous granules in prey varies between metals and type of granules. Similarly, the physicochemical form of accumulated Cd in Oligochaete worm, *Limnodrilus hoffmiesteri*, is critical in the assimilation of Cd by the predator *Palaemonetes pugio* [114,115].

Different groups of aquatic invertebrates behave differently with respect to essential and nonessential metals. Decapods usually regulate their body concentrations of essential elements such as Zn, Cu, and Fe to approximately constant levels [116,117], but they are net accumulators of nonessential elements Cd and Pb [116]. On the other hand, amphipods and barnacles are net accumulators (to different degrees) of Zn, Cu, Fe, Cd, and Pb [117].

Decapods such as prawns, which are an important food source inhabiting metal-contaminated sites, have elevated trace element concentrations due to high uptake rates of individual organisms

[118]. Differences in trace metal contents in tissues of different prawn species have been attributed to habitat differences (estuarine, marine, etc.) and also to contaminant levels and dietary shifts due to change in habitat types [118–121]. Changes in the trace element content in body tissues of aquatic biota have also been attributed to seasonal differences. Rapid growth of aquatic invertebrates at relatively high temperature leads to low concentration of non-essential metals such as Cd and Pb due to growth dilution. In penaid prawn (*Metapenaeopsis palmensis*) found in tropical coastal waters of Hong Kong, growth dilutes the Cd body concentration [122]. In contrast, typical Cd concentration in temperate caridean species is higher due to slower growth rates [123].

Bottom-dwelling aquatic fauna includes a wide diversity of organisms, including aquatic insects, benthic invertebrates, and bottom-dwelling fish species [124]. Sediments in aquatic ecosystems act as a source and sink for pollutants. Trace element concentration in the sediments is three to five orders of magnitude higher compared to that in the overlying water column [125]. The high levels of trace elements and their relatively high availability for uptake indicate that elements associated with sediments can pose a direct risk to benthic organisms [126]. The uptake of sediment-associated trace elements is largely a function of bioavailability in combination with physiological factors such as age and sexual condition [127]. Bioaccumulation of trace elements in benthic invertebrates such as lobsters has a great significance with respect to human health because lobster muscles are consumed by humans —thus, the indirect risk of trophic transfer of trace elements from benthic invertebrates.

Bioaccumulation of sediment-associated trace elements is highly species dependent because of diversity in feeding ecology and living habitats of benthic organisms [128]. Mode of feeding can significantly influence trace element bioaccumulation from sediments [129]. For example, deposit-feeding invertebrates may accumulate contaminants to a greater extent than filter feeders. Also, benthic organisms may preferentially select higher organic carbon sediments, thus influencing the exposure to sediment-associated contaminants [130]. Trace element bioaccumulation from sediments is influenced by metal speciation, transformation, metal–metal interactions, sediment chemistry, presence of metal–binding sites, and binding to dissolved organic matter [125].

It may be noted that physicochemical parameters of the water and sediments affect the bioavailability of trace elements to aquatic organisms. In particular, pH has a strong control on metal speciation because it determines the degree of metal hydrolysis, polymerization, aggregation, precipitation, and proton competition for available metal-binding sites or ligands [131]. Water hardness may influence metal accumulation by metal speciation and form insoluble organic and inorganic complexes that precipitate and become unavailable for bioconcentration [132,133]. Water hardness may also influence metal uptake independent of effect of metal speciation by inhibition of metal absorption and reduction in membrane permeability [134]. Metals can exist as free ions and inorganic complexes; this also influences their bioavailability.

32.2.2.2 Bioaccumulation in Fish and Trophic Transfer

Fish are ideal indicators of heavy metal contamination in aquatic ecosystems because they occupy different trophic levels [135]. Fish species bioaccumulate trace elements in different tissues, predominantly from their diet [136,137]. Many fish adapt to a wide variety of food sources and often switch from one food source to another as environmental and food supply conditions change [124]. Due to this capacity of trophic adaptability, trace element concentration in water and tissue trace element content do not have a consistent relationship. For example, fish from lakes with trace element levels below detection in water can carry trace element burdens that present a human health hazard. Yet, elevated concentration in water has also been measured in lakes where fish have a relatively low burden [138].

Trophic level differences in different fish species with respect to elemental content have been reported by a number of workers [139–142], although much of the work is with reference to mercury. In general, carnivorous species have higher levels than herbivorous, omnivorous, and

planktivorous species [143] and larger carnivores have higher levels than smaller carnivores. However, bottom-dwelling fish can sometimes have higher levels than carnivorous fish, particularly when they are ingesting sediments [144]. For example, Campbell [137] found that bottom-feeding redear sunfish (*Lepomis microlophus*) had higher levels than bass and bluegill sunfish, which are predominantly water-column feeders. Villar et al. [145] found a difference in the metal content in the tissues of the two fish species, *Prochilodus lineatus* (detritivore) and *Pterodoras granulosus* (omnivore). *P. lineatus* had a high concentration of metals in the tissues because it primarily fed on the metal-rich detritus. Thus, it is essential to understand the feeding location as well as the trophic level to understand contaminant levels.

Burger et al. [135] estimated trace element levels (As, Cd, Cr, Cu, Pb, Mn, Hg, and Sr) in 11 species of fish occupying different trophic levels with varied dietary habits. They found that species-specific differences existed in all the species studied with respect to all the trace elements. Bowfin and channel fish (both piscivores) had the highest level of all the elements except Mn and Sr. They also found that trophic relationships alone were not able to account for the elemental concentration in different fish species and suggested that metal levels in fish may also reflect age; older and larger fish have higher levels of trace elements. Such a correlation has been seen for mercury [146].

Stewart et al. [147] demonstrated the role of food web structure and physiology of trace element accumulation in the prey species in the differential bioaccumulation of trace elements by fish species; this resulted in some species of fish having very high concentrations of Se while others did not in the San Francisco Bay. Two dominant food webs present in the estuary region of the bay were based upon bivalves and crustacean zooplanktons. The dominant bivalve, *Potamocorbula amurensis,* had a tenfold slower rate of loss of Se from the body compared to that of the crustacean zooplanktons. This resulted in higher tissue Se concentration in the bivalves, which was then reflected in the higher tissue levels of Se in the predatory species of the bivalves. The tissue concentration far exceeded the threshold levels at which Se acted as teratogen and carcinogen, whereas concentration of Se in the predators of the zooplankton was less than the threshold value.

In this case, concentration of Se in water and sediments was not high (<1μg/lt), but in some of the top consumers like white sturgeon, the tissue levels were as high as >10 μg/g. This case is an example in which basic physiological and ecological processes can drive wide differences in exposure and effects among different species. These processes are rarely considered in traditional risk assessment studies of contaminant impacts. Besser et al. [148] also found that metal bioavailability to higher order consumers such as trout can be substantially modified by processing metals in the stream food web. Substantial variation in diets of higher consumers such as fish with respect to trace metal content exist due to differential accumulation of metals among invertebrate taxa and differences in taxonomic composition among different locations [149,150].

The differences in the bioaccumulation and trophic transfer potential of different trace elements may be related to their bioavailability in aquatic environments, chemical characteristics of the element, and food web processing of the element. Chen and Folt [138] found that, although As and Pb bioaccumulate in aquatic biota, the concentrations of both these elements biodiminish with increasing trophic levels. The elemental content in fish species was 10 to 20 times lower than what was present in the zooplanktons. Higher levels of As were present in planktivorous fish compared to the omnivores and piscivores. Kay [151] and Handy [152] concluded that Cd also did not biomagnify in the aquatic food web; however, methyl mercury had the capability to bioaccumulate and biomagnify in aquatic biota [135,153]. Besser et al. [148] found that Cd had a higher bioaccumlation factor compared to Pb, suggesting that Cd was highly available in the stream food web.

32.3 HUMAN EXPOSURE TO TRACE ELEMENTS

Exposure of the human population to trace elements occurs from multiple media (water, air, soil) and food. Estimation of exposure to trace elements from food is extremely complex due to varied dietary habits of human populations. Factors that influence dietary intake include age, sex, race,

residential region, ethnicity, and personal preferences [154]. Moreover, in metropolitan cities, the problem is further compounded by the fact that many food items comprising the diet of an average human are sourced from different places and not from a specific locality. The most important elements in terms of trophic transfer via the food chains to humans are As, Cd, Hg, and Pb [8].

32.3.1 Cadmium

Cd is a non-essential heavy metal occurring naturally in Zn and Pb ores [9]. Industrial uses of the metal and agricultural activities have led to widespread dispersion of this element in the environment and human food items. Studies have shown that the average concentration of trace elements in the general agricultural environment has increased over the years. Kjellstrom et al. [155] reported that the Cd content of Swedish wheat increased about threefold between 1900 and 1980. On similar lines, Jones et al. [156] found that the Cd content in the herbage grown in a semirural, undisturbed site in England almost doubled between 1860 and 1990.

One of the primary concerns with respect to cadmium is its transfer from agricultural produce to humans [157]. It is widely acknowledged that vegetable foods contribute to >70% of Cd intake of humans [158]. Accumulation and translocation of trace elements via the agricultural food chain depends upon soil and climatic factors, plant species (variety cultivated), and agronomic management practices [7,8,159]. As has already been discussed, the bioaccumulation of the trace elements can vary with the species and variety.

It is possible that, in some plant species, the edible portion might have low trace element content; however, dietary exposure is not only a function of the elemental content of the plant part consumed and also of the amount of the tissue consumed. For example, even though reproductive structures of flowering plants, such as grains, have relatively low elemental content compared to the other plant tissues, they are consumed in relatively large amounts [157] and therefore contribute largely to the dietary exposure [154]. Cd levels in most vegetables, including bulbs, roots, and tubers, are usually below 0.05 mg/kg, although leafy vegetables such as spinach and lettuce may have considerably higher levels [160]. Most plant-based food stuffs contain higher Cd concentration of approximately 25 μg/kg fresh weight, which represents food items such as cereals, root tubers, and vegetables [7].

Cadmium content in muscle meats is relatively low. In contrast, cadmium content in visceral meats (kidney, liver, and pancreas) is high because these organs preferentially accumulate Cd and other non-essential elements in the animal body [161]. The Cd levels in muscle meats are of the order of 0.01 mg/kg for slaughter animals [7]; cadmium content in the liver and kidney of calves, pigs, and poultry ranges from 0.02 to 0.2 mg/kg and 0.05 to 0.5 mg/kg, respectively.

Aquatic food species (fish, crab, oysters, etc.) bioconcentrate Cd and therefore can have high Cd concentrations [157]. Typical Cd concentration reported in fish muscle is about 0.02 mg/kg, although higher levels may also be found in some fish species. Certain other sea foods may also accumulate Cd from contaminated waters. Certain shell fish can have Cd content in excess of 50 – 100 μg/g fresh weight [7]. Although milk has moderate Cd concentration it is a major source of Cd for infants and children, contributing about 50 and 25% of Cd intake for bottle-fed and breast-fed infants, respectively [158,162]. A number of studies have been carried out to estimate the exposure of the human newborn to Cd via breast feeding [162–164].

Mean daily intake of Cd from food in developed countries has been estimated to be in the range of 16 to 60 μg/day [165]. The provisional tolerable weekly intake (PTWI) of Cd is 7 μg/kg of body weight per week or 1 μg/kg of body weight per day [166]. It may be noted that the safety margin between the exposure in normal diet and the level of exposure that produces deleterious effects is very low.

People who habitually consume a diet high in Cd — for example, due to high consumption of shellfish and sea food — are of particular concern. Bioavailability of Cd from various foods is not well understood. Factors that may influence bioavailability include the chemical form of Cd-

consumed tissue, content of competing ions and ligands in the diet, effects of food preparation methods, and the nutritional state of the consuming animal [157].

Database estimation of dietary Cd intake probably provides a reasonable method for estimating relative contributions of different food groups to dietary Cd intake, but its use in health risk assessment is doubtful. Its use in health risk assessment should be validated by analysis of duplicated diets. In a study in the U.S., the database calculation gave an estimate of Cd intake to about 24 μg/day; however, an actual analysis of duplicate diets estimated intake at 56 μg/day [167].

32.3.2 Mercury

Mercury is ubiquitous in the environment and derives from natural and anthropogenic sources. In nature, it is present in three different forms: elemental mercury (Hg0), inorganic mercury compounds (I-Hg), and organic mercury (primarily methyl mercury, MeHg) [12]. Speciation of Hg is critical in determining the toxicity of different forms of Hg, of which methyl mercury is the most toxic and also the most important with respect to dietary exposure to humans [168]. Inorganic Hg deposits in aquatic environments and is converted through methylation to MeHg by microorganisms [169]. Methyl mercury is readily bioaccumulated and transferred in the aquatic food web with a tendency for biomagnification resulting in high concentration in predatory fish and aquatic wildlife [12].

Fish are the primary source of methyl mercury in the human diet [170]. Nearly all of the mercury present in the fish muscle is in the form of methyl mercury [171]. The dietary uptake of methyl mercury in fish is influenced by their size, diet, and trophic position [172,173]. Estimated concentration of mercury in 3-year-old large-mouth bass collected from 53 lakes in Florida in the U.S. varies form 0.04 to 1.53 μg/g wet weight [174]. Methyl mercury content was highest in long-lived, larger fish that feed on other fish, such as tile fish, king mackerel, sword fish, and shark (Table 32.2).

In humans, 90 to 100% of Me Hg is absorbed through the gastrointestinal tract, where it easily enters the blood stream and distributes through the body [12]. The reference dose set by the U.S. Environmental Protection Agency for ingested methyl mercury exposure is 0.1 μg/kg body weight per day. It has been suggested that a food preparation factor should be used in risk assessment because, when the fish is cooked (especially deep-frying), the concentration of Hg in micrograms per kilogram increases, although the cooked fish retains the same amount of Hg as was present in the raw fish [175,176].

TABLE 32.2
Mean and Range of Mercury (Hg) in Different Seafood Species

Species	Mean (ppm)	Range (ppm)
Northern lobster (American)	0.31	0.05–1.31
King crab	0.09	0.02–0.63
Tuna (fresh or frozen)	0.32	ND–1.30
Shrimp	ND	ND
Catfish	0.07	ND–0.31
Tilefish	1.45	0.65–3.73
Sword fish	1.00	0.10–3.22
King mackerel	0.73	0.30–1.67
Shark	0.96	0.05–4.54

Notes: ND: not detectable. Data from U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Seafood (May 2001).

Source: Adapted from Counter, S.A. and Buchanan, L.H., *Toxicol. Appl. Pharmacol.*, 198, 209, 2004.

In the U.S., 41 states have issued advisories on limiting fish intake, especially for pregnant women and women who may become pregnant [177]. It may be noted that methyl mercury exposure during fetal development and breast feeding is strongly related to the maternal Hg burden [178]. Maternal constitution factors that affect Hg secretion into breast milk are maternal age and lactation stage [179].

Mercury concentration in food crops is generally low, with most of the dietary intake of Hg deriving from consumption of seafood. Exposure of mercury through food items other than fish contaminated with methyl mercury is much less via trophic transfer. Concentration of mercury in most other food items in the average human diet is below the detection limit (20 μg/kg fresh weight) [180,181]. Levels of Hg in most field crops are sufficiently low to cause any concern from the human health viewpoint [182]. This is because mercury is strongly sorbed to soil constituents and as Hg^{2+} or hydrolyzed species is rather immobile in soils [159]. Mercury poisoning on account of consumption of agricultural crops reported in Iraq was due to the consumption of seeds treated with mercury fungicides and not trophic transfer [183].

32.3.3 Lead and Arsenic

Industrial and vehicular pollution are primary sources of contamination of air, water, soil, and food [184]. The major source of lead for nonoccupationally exposed humans is through food and water [7,168]. The amount of lead in food crops depends upon the uptake of lead from the contaminated soils by the plants. Lead is strongly retained by most soils, resulting in very low soil solution Pb concentration compared to other elements such as Cd [185]. Lead content is more in the roots than in the stems and leaves; seeds and fruits have the lowest concentration. Pb concentration in crops is generally well within guidelines or regulatory levels set by respective countries (Table 32.3) [159].

Particulate lead can deposit on the leaf surfaces due to atmospheric fallout of the element. Lead content in dairy products ranges from 0.003 to 0.083 μg/g; vegetables have 0.005 to 0.65 μg/g and meat, fish, and poultry products have 0.002 to 0.16 μg/g [7]. Lead exposure can be further enhanced by domestic food processing, such as food canning, serving of food in glazed pottery, and delivery of water from lead pipes [186]. Because of detrimental effects of lead on the developing infant central nervous system [187], studies have been carried out on the lead levels in human breast milk [163,168]. The WHO considers 2 to 5 ng/g of Pb in human milk "normal" [188]. Diet is the main

TABLE 32.3
Lead Concentrations in Some Field Crops

	Mean (mg/kg fresh range weight)		
Crop/country			**Ref.**
Wheat:			
The Netherlands	0.16	0.03–0.65	182
U.S. (all states)	0.037	<0.001–0.716	245
Carrots:			
The Netherlands	0.05	0.011–0.21	182
U.S. (all states)	0.009	0.001–0.125	245
Onions:			
The Netherlands	0.02	0.009–0.05	182
U.S. (all states)	0.005	<0.002–0.054	245
Spinach:			
The Netherlands	0.09	0.01–0.29	182
U.S. (all states)	0.045	0.016–0.17	245

Source: Adapted from McLaughlin, M.J. et al., *Field Crops Res.*, 60, 143, 1999.

source of maternal exposure to Pb [189]. Moreover, during pregnancy and lactation, Pb is mobilized from the bones and is likely to result in increased concentration of lead in blood and breast milk, with potentially toxic effects on the fetus and the mother [190].

Arsenic occurs in food, air, water, and soil, and practically all human populations are exposed to As in one form or another. The major sources of exposure to As are food and water [9]. The principal cause of elevated soil As is the widespread use of As compounds as insecticides, herbicides, and defoliants for agriculture [159]. Arsenic also enters the soil by mining and smelting of nonferrous metals, application of phosphate fertilizers, fossil fuel combustion, and application of municipal sewage sludge [191]. All these sources include inorganic salts and various organic compounds of arsenite As (III) and arsenate As (V).

The degree of toxicity and the resulting pathologic states depend upon the chemical form of arsenic present in food items [192]. Food contains organic and inorganic forms of arsenic [159], whereas drinking water predominantly has inorganic arsenic [193]. In terms of dietary exposure of As to humans, organo–As compounds found in seafood dominate. Consequently, the total human intake of arsenic depends upon the quantity of seafood consumed [194]. Marine animals have a limited ability to bioconcentrate inorganic As from sea water, but they can bioaccumulate organo–arsenic compounds. Falconer et al. [195] detected arsenic concentrations ranging from 12 to 216 μg/g in *Pleuronectes platessa* from the North Sea. Food crops have highly variable and intermediate percentages of such compounds [159]. Organo–As compounds are absorbed readily from the gastrointestinal tract, but are not metabolized in the body and readily excreted out. It is inorganic As (III) and As (V) that pose a greater health risk.

32.4 HUMAN HEALTH EFFECTS

Human health effects associated with trophic transfer are of diseased states associated with chronic rather than acute exposure to trace elements. Research on the health effects of chronic exposure to trace elements suggests that physiological alterations may occur at levels that were formerly considered to be safe [8]. Neurological and neurophysiological effects, nephrotoxicity, reproductive toxicity, teratogenicity, and carcinogenicity remain at the forefront of research on the health effects of trace elements [196,197].

32.4.1 Cadmium

Cadmium can cause irreversible renal tubular injury, nonhypertrophic emphysema, osteoporosis, anemia, eosinophelia, anosmia, and chronic rhinitis [157,158,198]. The sentinel sign of Cd adverse effect is renal tubular dysfunction, which is characterized by low molecular weight proteinuria [199] and can occur in concert with anemia [200,201] or bone mineral loss [202,203]. Renal tubular dysfunction caused due to Cd exposure is generally irreversible and can constitute a significant health effect [92,158]. In a study of nearly 1700 subjects aged between 20 and 80 years, sampled randomly from the general population of four areas of Belgium having various levels of exposure to industrially derived Cd pollution, it was concluded that 10% of the Belgian population absorb sufficient Cd to cause renal dysfunction [204].

Recently, an association between cadmium exposure and chronic renal failure (end stage renal disease, ESRD) was shown [205]. Elevated levels of Cd in the diet and drinking water were concluded to be causative factors in the 1964 occurrence of Itai Itai disease in Toyoma prefecture in Japan [206]. The source of the Cd was acid drainage from a Pb–Zn–Cd mine into the Jintsu River. Water from the river was used for drinking and irrigation of the rice paddies. Cd intake from food and water was estimated to be 300 to 600 μg/day [158]. The disease was characterized by severe pain, bone fractures, proteinuria, and severe osteomalacia, which appeared mainly among women. Exposure to low doses of Cd has led to decreases in the density of bone tissue [207,208].

Cadmium exposure also enhances susceptibility to bacterial, protozoal, and viral infections and results in impaired and humoral and cell-mediated immune response [209].

Several groups of individuals have been identified as "at risk" from excess Cd exposure, including: persons having severe nutritional deficiencies (Fe, Ca, Zn, protein, vitamin D) that are aggravated by Cd; persons consuming more than normal levels of visceral meats, fish, and shellfish; pregnant and lactating females with a negative Ca balance; nursing infants; persons with kidney ailments; and multiparous, postmenopausal women [158,210,211].

The International Agency for Research on Cancer (IARC) has classified cadmium as a human carcinogen (group I) on the basis of sufficient evidence in humans and experimental animals [212]. Cadmium has been associated with cancer of the lung, prostrate, pancreas, and kidney. It is predominantly a nongenetic carcinogen. Many indirect mechanisms are implicated in carcinogenicity of Cd, such as modification of gene expression and signal transduction, interference with enzymes of the cellular antioxidant system and generation of reactive oxygen species, inhibition of DNA repair, DNA methylation, role in apotopsis, and disruption of E-cadherin-mediated cell–cell adhesion [198].

32.4.2 Mercury

Health effects of mercury are highly dependent on the different forms mercury. Methyl mercury is the most toxic form because of its neurotoxic properties [213]. In humans, the main target for mercury, especially methyl mercury, is the central nervous system; exposure to methyl mercury can cause serious brain damage, including psychological disturbances, impaired hearing, loss of sight, ataxia, loss of motor control, and general debilitation [214]. In humans, 90 to 100% of methyl mercury is absorbed through the gastrointestinal tract from which it enters the blood stream and is distributed throughout the body [12]. It is transported across the blood–brain barrier by an amino acid carrier and readily accumulates in the brain [215].

Although methyl mercury is distributed across the body, its most serious effects are on the developing brain. In adult brain, methyl mercury damage is focal — for example, involving loss of neurons in the visual cortex and loss of granule neurons in the cerebellum. In the developing brain, the damage is more diffuse and extensive [12]. Methyl mercury affects the formation of microtubules and thus neuronal migration and cell division [170,213,216]. The earliest symptoms are parestias and numbness in hands and feet. Later, coordination difficulties and concentric constriction of visual fields may develop with auditory symptoms. At high exposure levels, methyl mercury may result in a loss of neurons in each lobe of the brain, and the developmental effects may include hyperactive reflexes, deafness, blindness, cerebral palsy, mental retardation, and general paralysis [183,217].

At low exposure levels, the neurodevelopmental effects may be subtle and include deficits in language, learning, attention, and, to a lesser degree, fine motor and visual–spatial organizational impairments. Several possible molecular targets of methyl mercury exposure in the nervous system include the blood–brain barrier, cytoskeleton, axonal transport, neurotransmitter production, secretion, uptake and metabolism cell signaling, protein, DNA and RNA synthesis, and respiratory and energy-generating systems [216].

The Minamata catastrophe in Japan in the 1950s was caused by methyl mercury poisoning from fish contaminated by mercury discharges to the surrounding sea. In the early 1970s, more than 10,000 persons in Iraq were poisoned by eating bread baked from mercury-polluted grain [9]. Gender-related susceptibility of Me Hg neurotoxicity has been extensively studied, but only some evidence indicates that women are more affected than men when exposure occurs in adulthood [218]. Males seem to be more affected by exposure during stages of early development [219,220]. Sakamota et al. [221] found that a declining male birth ratio was associated with increased male fetal death due to Me Hg exposure in Minamata, Japan. Methyl mercury and inorganic Hg can also induce DNA strand breaks in cells [222] and inhibit DNA repair. Although, some evidence indicates

that inorganic and methyl mercury can cause renal tumors in rodents, evidence for carcinogenicity of Hg in humans is inadequate [223].

32.4.3 Lead

Occupational and environmental chronic Pb exposure can damage the central nervous system, kidneys, and cardiovascular, reproductive, and hematological systems [224]. Gastrointestinal absorption of Pb varies with age, diet, and nutritional status. Age is a critical variable in absorption levels, with adults absorbing 7 to 15% from dietary sources; in infants and children, absorption levels can reach 40 to 50% [225]. Chronic exposure of Pb follows a prolonged disease progression. Long-term exposure can lead to distal motor neuropathy, possible seizures, and coma [8]. Infants and young children have long been known to be at risk to toxicity of Pb because of higher Pb intake relative to body size and greater absorption from the gastrointestinal tract. The central nervous system of the developing fetus may be at even greater risk because of immaturity of the blood–brain barrier [226].

A number of cross-sectional studies and prospective epidemiological studies have shown impairment of cognitive behavioral development in children [224]. In acute toxicity, lead can also induce encephalopathy in children, with symptoms of headache, confusion, stupor, coma, and seizures [226]. It is suggested that immature endothelial cells forming the capillaries in the developing brain are less resistant to the effects of Pb than capillaries from mature brain are. These cells permit fluid and cations, including Pb, to reach newly formed components of the brain, particularly astrocytes and neurons [227]. Pb also produces deficits in neurotransmission through inhibition of cholinergic function, possibly by reduction of extracellular Ca [226].

Overt effects of lead on the kidney in man and experimental animals, particularly rat and mouse, begin with acute morphological changes consisting of nuclear inclusion bodies or lead–protein complexes and ultrasructural changes in organelles, particularly mitochondria. Progression of acute nephropathy to chronic irreversible nephropathy occurs slowly, over months or years, and only after years of heavy exposure [226]. Experimental studies suggest a possible threshold for lead nephrotoxicity. Mortada et al. [228] found that long-term Pb exposure may also give rise to kidney damage. It was found that blood lead level of 60 μg/dL is the threshold for proximal tubular cell injury from lead [229].

Buchet et al. [231] found that workers who did not have lead levels of over 62 to 63 μg/dL for up to 12 years did not have Pb nephropathy. It has also been recognized that severe Pb intoxication is associated with sterility, abortion, still births, neonatal morbidity, and mortality from exposure *in utero* [230]. Effects of Pb on the hematological system have also been known for a long time. Anemia is a well known symptom of Pb poisoning; Pb inhibits activity of γ-aminolevulinic acid dehydratase (ALAD) and ferrochetalase, which are involved in heme synthesis, and also leads to changes in RBC morphology and survival [231].

More than 90 % of the body burden of Pb is localized in the bone, with an average half-life of about 10 years [224]. The accumulated Pb in bone tissue follows the same general physiology as that of bone Ca metabolism [232]. During periods like pregnancy and lactation, bone Pb stores may be mobilized even long after cessation of exposure [233,234]. Endogenous exposure of Pb may occur during the critical period of organ development in the fetus and nursing child. Roussow et al. [235] found that exposure to Pb *in utero* resulted in sixfold increase in brain accumulation as compared to 3.5- to 2-fold increase during other periods. Some evidence indicates that certain genetic and environmental factors can increase the detrimental effects of Pb on neural development, thereby rendering certain children more vulnerable to Pb neurotoxicity [236]. Pb has direct and indirect effects on bone turnover. Indirect effects of Pb are via kidney dysfunction and inhibition of 1,25-dihydroxy vitamin D3; direct effects are on osteoblast and osteoclast functions and inhibition of synthesis of bone matrix components [226,232].

32.4.4 Arsenic

The toxicity of As varies with its chemical state, ranging from virtually nontoxic forms of organic and pure elemental arsenic to acutely toxic trivalent arsenic trioxide. Organo–As compounds, which have a potential for bioaccumulation and trophic transfer, have relatively reduced human health risk associated with them. Predominantly, health risk is associated with exposure to inorganic As (II) and As (V) through drinking water. The existing drinking water limit for As is 50 μg/lt; some evidence indicates that the permissible limit must be lowered because carcinogenicity has been observed at As levels less than an order of magnitude from the drinking water limit [11].

Epidemiological data have shown that chronic exposure of humans to inorganic arsenical compounds is associated with liver injury, peripheral neuropathy, and increased incidence of cancer of lung, skin, bladder, and liver [9,237]. Arsenic can also cross the placenta and can cause fetotoxicity, decreased birth weight, and congenital malformation [196]. Several mechanisms have been implicated in arsenic-induced genotoxicity, which includes oxidative stress [238,239]. DNA repair inhibition [240,241] and direct mutagenesis [242] have been reported. In humans, an increased percentage of apoptosis was found in the buccal epithelial cells from individuals chronically exposed to arsenic in China [243]. Inorganic arsenic is a known human carcinogen causing lung cancer by inhalation and skin cancer via ingestion [244].

32.5 CONCLUSIONS

Anthropogenic activities such as mining, smelting, and combustion of fossil fuels have altered the biogeochemical cycles of many trace elements dramatically. This has resulted in increased trace element content in environmental resources (land, air, and water) and biota. Bioaccumulation of trace elements by living organisms is influenced by the chemical attributes of the trace element, physicochemical characteristics of the ambient environment, physiological make up of the organism, and ecological host factors. The increasing level of trace elements in the tissues of plants and animals due to bioaccumulation and trophic transfer has adverse effects on ecological and human health.

Human beings are top consumers of many terrestrial and aquatic food chains; this results in exposure to trace elements due to consumption of contaminated plant and animal products sourced form biota with elevated trace element content. Dietary exposure is affected by dietary preferences (choice of food items), age, sex, residential region, and ethnicity, among other things; the assimilation of the ingested trace elements is influenced by nutritional status, metal–metal interactions, and the chemical form of the element in the ingested food. Trace elements vary with respect to their potential for trophic transfer to humans via food; elements such as cadmium and methyl mercury are probably the most important with respect to their ability for trophic transfer and potential effects on human health.

Current advances in key areas, such as bioavailability; uptake; assimilation and tissue distribution; detoxification mechanisms of trace elements at the organismal level; and the role played by the ecological characteristics such as food chain length, foraging behavior, and feeding ecology, have led to a better understanding of the variability in the host and environmental factors affecting trace element cycling. These advances are critical for ecological risk assessment and also provide information on variability of trace elements in different constituents of the human diet.

Recent data have indicated that the adverse health effects related to trace element exposure occur at lower levels than previously expected. In this regard, it is essential to identify the risk factors associated with the trace element exposure and to identify risk groups in human populations in order to achieve a reliable risk assessment. Finally, better ways should be developed to put the advances in the body of knowledge with respect to trace elements into risk assessment and regulatory practice to minimize the ecological and health risks associated with trace element exposure.

ACKNOWLEDGMENT

A.L. received a research fellowship from the Council of Scientific and Industrial Research, India.

REFERENCES

1. Brown, G.E., Jr., Foster, A.L., and Ostergren, J.D., Mineral surfaces and bioavailability of heavy metals: a molecular-scale perspective, *Proc. Nat. Acad. Sci. USA*., 96, 3388, 1999.
2. Nriagu, J.O. and Pacyna, J.M., Quantitative assessment of worldwide contamination of air, water and soils by trace metals, *Nature*, 333, 134, 1988.
3. McGrath, S.P., Zhao, F.J., and Lombi, E., Plant and rhizosphere processes involved in phytoremediation of metal-contaminated soils, *Plant Soil*, 232, 207, 2001.
4. Meagher, R.B., Phytoremediation of toxic elemental and organic pollutants, *Curr. Opin. Plant Biol*., 3, 153, 2000.
5. Pierzynski, G.M., Sims, J.T., and Vance, G.J., *Soils and Environmental Quality*, 2nd ed., CRC Press, Boca Raton, FL, 2000, 19.
6. Underwood, E.J., Trace elements and health: an overview, *Phil. Trans. R. Soc. Lond. B*., 288, 5, 1979.
7. Rojas, E., Herrera, L.A., Poirier, L.A., and Ostrosky–Wegman, P., Are metals dietary carcinogens? *Mut. Res*., 443, 157, 1999.
8. Robson, M., Methodologies for assessing exposures to metals: human host factors, *Ecotox. Environ. Safety*, 56, 104, 2003.
9. Jarup, L., Hazards of heavy metal contamination, *Brit. Med. Bull*., 68, 167, 2003.
10. Ercal, N., Gurer–Orham, H., and Aykin–Burns, N., Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage, *Curr. Topics Med. Chem*., 1, 529, 2001.
11. Schoen, A., Beck, B., Sharma, R., and Dube, E., Arsenic toxicity at low doses: epidemiological and mode of action considerations, *Toxicol. Appl. Phamacol*., 198, 253, 2004.
12. Counter, S.A. and Buchanan, L.H., Mercury exposure in children: a review, *Toxicol. Appl. Pharmacol*., 198, 209, 2004.
13. Peterson, B.J. and Fry, B., Stable isotopes in ecosystem studies, *Ann. Rev. Ecol. Sys*., 18, 293, 1987.
14. Cabana, G. and Rasmussen, J.B., Modeling food chain structure and contaminant bioaccumulation using stable nitrogen isotopes, *Nature*, 372, 255, 1994.
15. Torres, K.C. and Johnson, M.L., Bioaccumulation of metals in plants, arthropods, and mice at a seasonal wetland, *Environ. Toxicol. Chem*., 20, 2617, 2001.
16. Newman, M.C., *Fundamentals of Ecotoxicology*, Ann Arbor Press, Chelsea, MI, USA, 1998, 71.
17. Gnamus, A., Byrne, A.R., and Horvat, M., Mecury in the soil-plant-deer-predator food chain of a temperature forest in Solvenia, *Environ. Sci. Technol*., 34, 3337, 2000.
18. Cataldo, D.A., Wildung, R.E., and Garland, T.R., Speciation of trace inorganic contaminants in plants and bioavailability to animals: an overview, *J. Environ. Qual*., 16, 289, 1987.
19. Peakall, D. and Burger, J., Methodologies for assessing exposure to metals: speciation, bioavailability of metals, and ecological host factors, *Ecotox. Environ. Safety*, 56, 110, 2003.
20. John, M.K., van Laerhoven, C.J., and Chuah, H.H., Factors affecting plant uptake and phytotoxicity of cadmium added to soils, *Environ. Sci. Technol*., 6, 1005, 1972.
21. Kuboi, T., Noguchi, A., and Yazaki, J., Family-dependent cadmium accumulation characteristics in higher plants, *Plant Soil*, 92, 405, 1986.
22. Xian, X., Effect of chemical forms of cadmium, zinc, and lead in polluted soils on their uptake by cabbage plants, *Plant Soil*, 113, 257, 1989.
23. Cataldo, D.A. and Wildung, R.E., The role of soil and plant metabolic processes in controlling trace element behavior and bioavailability to animals, *Sci. Total Env*., 28, 159, 1983.
24. Darrah, P.R. and Stauton, S., A mathematical model of root uptake incorporating root turnover, distribution within the plant and recycling of absorbed species, *Eur. J. Soil Sci*., 51, 643, 2000.
25. Waisel,Y., Eshel, A., and Kafkafi, U., *Plant Roots: The Hidden Half*, 3rd ed., Marcel Dekker Inc., New York, 2002, 617.

26. Hinsinger, P., Bioavailability of trace elements as related to root-induced chemical changes in the rhizosphere, in *Trace Elements in the Rhizosphere*, Gobran, G.R., Wenzel, W.W., and Lombi, E., Eds., CRC Press, Boca Raton, FL, 2001, 25.
27. Pinel, F., Leclerc–Cessac, E., and Staunton, S., Relative contributions of soil chemistry, plant physiology and rhizosphere induced changes in speciation on Ni accumulation in plant shoots, *Plant Soil*, 255, 619, 2003.
28. Knight, B., Zhao, F.J., McGrath, S.P., and Shen, Z.G., Zinc and cadmium uptake by the hyperaccumulator *Thlaspi caerulescens* in contaminated soils and its effects on the concentration and chemical speciation of metals in soil solution, *Plant Soil*, 197, 71, 1997.
29. McGrath, S.P., Shen, Z.G., and Zhao, F.J., Heavy metal uptake and chemical changes in the rhizosphere of *Thlaspi caerulescens* and *Thlaspi ochroleucum* grown in contaminated soils, *Plant Soil*, 188, 153, 1997.
30. Whiting, S.N., de Souza, M.P., and Terry, N., Rhizosphere bacteria mobilize Zn for hyperaccumulation by *Thlaspi caerulescens*, *Environ. Sci. Technol*., 35, 3144, 2001.
31. Whiting, S.N., Leake, J.R., McGrath, S.P., and Baker, A.J.M., Zinc accumulation by Thlaspi caerulescens from soils with different Zn availability: a pot study, *Plant Soil*, 236, 11, 2001.
32. Abou–Shanab, R.A., Angle, J.S., Delorme, T.A., Chaney, R.L., van Berkum, P., Mowad, H., Ghanem, K., and Gozlan, H.A., Rhizobacterial effects on nickel extraction from soil and uptake by *Alyssum murale*, *New Phytol*., 158, 219, 2003.
33. Killham, K. and Firestaone, M.K., Vesicular-arbuscular mycorrhizal mediation of grass response to acidic and heavy metal deposition, *Plant Soil*, 72, 39, 1983.
34. Heggo, A., Angle, J.S., and Chaney, R.L., Effect of vesicular–arbuscular mycorrhizae fungi on heavy metal uptake by soybeans, *Soil Biol. Biochem*., 22, 865, 1990.
35. Tam, P.C.F., Heavy metal tolerance by ectomycorrhizal fungi and metal amelioration by *Pisolithus tinctorium*, *Mycorrhiza*, 5, 181, 1995.
36. Leyval, C. and Joner, E.J., Bioavailability of heavy metals in the mycorrhizosphere, in *Trace Elements in the Rhizosphere*, Gobran, G.R., Wenzel, W.W., and Lombi, E., Eds., CRC Press, Boca Raton, FL, 2001, 165.
37. Burd, G.I., Dixon, D.G., and Glick, B.R., A plant growth-promoting bacterium that decreases nickel toxicity in seedlings, *Appl. Environ. Microbiol*., 3663, 64, 1998.
38. Podar, D., Ramsey, M.H., and Hutchings, M.J., Effect of cadmium, zinc and substrate heterogeneity on yield, shoot metal concentration and metal uptake by *Brassica juncea*: implications for human health risk assessment and phytoremediation, *New Phytol*., 163, 313, 2004.
39. John, M.K. and van Laerhoven, C.J., Differential effects of cadmium on lettuce, *Environ. Pollut*., 10, 163, 1976.
40. Baker, A.J.M., Accumulators and excluders — strategies in the response of plants to heavy metals, *J. Plant Nutr*., 3, 643, 1981.
41. Landberg, T. and Greger, M., Can heavy metal-tolerant clones of *Salix* be used as vegetation filters on heavy metal-contaminated land? In *Willow Vegetation Filters for Municipal Wastewater and Sludges: a Biological Purification System*, Aronsson, P. and Perttu, K., Eds., Swedish University of Agricultural Sciences, Uppsala, 1994, 133.
42. Berthelsen, B.O., Steinnes, E., Solberg, W., and Jingsen, L., Heavy metal concentrations in plants in relation to atmospheric heavy metal deposition, *J. Environ. Qual*., 24, 1018, 1995.
43. Broadley, M.R., Willey, N.J., Wilkins, J.C., Baker, A.J.M., and White, P.J., Phylogenetic variation in heavy metal accumulation in angiosperms, *New Phytol*., 152, 9, 2001.
44. Nan, Z., Li, J., Zhang, J., and Cheng, G., Cadmium and zinc interactions and their transfer in soil-crop system under actual field conditions, *Sci. Total Environ*., 285, 187, 2002.
45. Lubben, S. and Sauerbeck, D., The uptake and distribution of heavy metals in spring wheat, *Water Air Soil Pollut*., 57–58, 239, 1991.
46. Brooks, R.R., Lee, J., Reeves, R.D., and Jaffre, T., Detection of nickeliferous rocks by analysis of herbarium specimens of indicator plants, *J. Geochem. Explor*., 7, 49, 1977.
47. Brooks, R.R., Geobotany and hyperaccumulators, in *Plants that Hyperaccumulate Heavy Metals*, Brooks, R.R., Ed., CAB International, Wallingford, U.K., 1998, 55.

48. Baker, A.J.M., McGrath, S.P., Reeves, R.D., and Smith J.A.C., Metal hyperaccumulator plants: a review of the ecology and physiology of a biochemical resource for phytoremediation of metal-polluted soils, in *Phytoremediation of Contaminated Soil and Water*, Terry, N., Banuelos, G., and Vangronsveld, J., Eds., Lewis Publishers, Boca Raton, FL, 2000, 85.
49. Baker, A.J.M., Reeves, R.D., and Hajar, A.S.M., Heavy metal accunulation and tolaerance in British population of the mettalophyte *Thlaspi caerulescens* J. and C. Presl (Brassicaceae), *New Phytol*., 127, 61, 1994.
50. Shen, Z.G., Zhao, F.J., and McGrath, S.P., Uptake and transport of Zn in the hyperaccumulator *Thlaspi caerulescens* and the nonhyperaccumulator *Thlaspi ochroleucuns*, *Plant Cell Environ*., 20, 898, 1997.
51. Rapport, D.J., What constitutes ecosystem health? *Perspect. Biol. Med*. 33, 120, 1989.
52. Peakall, D.B., *Animal Markers as Pollution Indicators*, Chapman & Hall, London, 1992.
53. Burger, J. and Gochfeld, M., Heavy metal and selenium concentrations in eggs of Herring gulls (*Larus argentatus*): temporal differences from 1989 to 1994, *Arch. Environ. Contam. Toxicol*., 29, 192, 1995.
54. O'Brien, D.J., Kaneene, J.B., and Poppenga, R.H., The use of mammals as sentinels for human exposure to toxic contaminants in the environment, *Environ. Health Perspect*., 99, 351, 1993.
55. Talmage, S. and Walton, B.T., Small mammals as monitors of environmental contaminants, *Rev. Environ. Contam. Toxicol*., 119, 47, 1991.
56. McBee, K. and Bickham., J.W., Mammals as bioindicators of environmental toxicity, in *Current Mammology*, Geoways, H.H., Ed., vol. 2, Plenum Press, New York, 1990, 37.
57. Reinecke, A.J., Reinecke, S.A., Musilbono, D.E., and Chapman, A., The transfer of lead from earthworms to shrews (*Myosorex varius*), *Arch. Environ. Contam. Toxicol*., 39, 392, 2000.
58. Burger, J., Metals in avian feathers: bioindicators of environmental pollution, *Rev. Environ. Toxicol*., 5, 203, 1994.
59. Attuquayefio, D.K., Gorman, M.L., and Wolton, R.J., Home range sizes in wood mouse *Apodemus sylavticus* habitat, sex and seasonal differences, *J. Zool*., 210, 45, 1986.
60. Marinussen, M.P.J.C. and Vanderzee, S.E.A.T.M., Conceptual approach to estimating the effect of home range on the exposure of organism to spatially variable soil contamination, *Ecol. Model*., 87, 83, 1996.
61. Larison, J.R., Likens, G.E., Fitzpatrick, J.W., and Crock, J.G., Cadmium toxicity among wildlife in Colorado Rocky Mountains, *Nature*, 406, 181, 2000.
62. Metcheva, R., Teodorova, S., and Topashka–Ancheva, M., A comparative analysis of the heavy metal loading of small mammals in different regions of Bulgaria I: monitoring points and bioaccumulation features, *Ecotox. Environ. Saf.*, 54, 176, 2003.
63. Hunter, B.A. and Johnson, M.S., Food chain relationships of copper and cadmium in contaminated grassland ecosystems, *Oikos*, 38, 108, 1982.
64. Cooke, J.A. and Johnson, M.S., Cadmium in small mammals, in *Environmental Contaminants in Wildlife: Interpreting Tissue Concentration*, Beyer, W.N., Heinz, G., and Redmond–Norwood, A., Eds., Lewis Publishers, Boca Raton, FL, 1996, 377.
65. Mertens, J., Luyssaert, S., Verbeeren, S., Vervaeke, P., and Lust, N., Cd and Zn concentrations in small mammals and willow leaves on disposal facilities for dredged material, *Environ. Pollut*., 115, 17, 2001.
66. Ma, W., Lead in mammals, in *Environmental Contaminants in Wildlife: Interpreting Tissue Concentration*, Beyer, W.N., Heinz, G., and Redmond–Norwood, A., Eds., Lewis Publishers, Boca Raton, FL, 1996, 281.
67. Hunter, B.A., Johnson, M.S., and Thompson, D.J., Ecotoxicology of copper and cadmium in a contaminated grassland ecosystem: small mammals, *J. App. Ecol*., 24, 601, 1987.
68. Watts, C.H.S., The foods eaten by wood mice (*Apodemus sylvaticus*) and bank voles (*Clethrionomys glareolus*) in Wytham Woods, Berkshire, *J. Animal Ecol*., 37, 25, 1968.
69. Erry, B.V. et al., Arsenic contamination in wood mice (*Apodemus sylvaticus*) and bank voles (*Clethrionomys glareolus*) on abandoned mine sites in southwest Britain, *Environ. Pollut*., 110, 179, 2000.
70. Beyer, W.N., Connor, E.E., and Gerould, S., Estimates of soil ingestion by wildlife, *J. Wildlife Manage*., 58, 375, 1994.
71. Shore, R.F., Predicting cadmium, lead and fluoride levels in small mammals from soil residues and by species–species extrapolation, *Environ. Pollut*., 88, 333, 1995.

72. Sharma, R.P. and Shupe, J.L., Lead, cadmium and arsenic residues in animal tissues in relation to those in their surrounding habitats, *Sci. Total Environ*., 7, 53, 1977.
73. Purcell, P.W., Hynes, M.J., and Fairley, J.S., Lead levels in small Irish rodents (*Apodemus sylvaticus* and *Clethrionomys glareolus*) from around a tailing pond and along motorway verges, *Proc. Royal Irish Acad.*, 92B, 79, 1992.
74. Lodenius, M., Soltanpour–Gargari, A., Tulisalo, E., and Henttonen, H., Effects of ash application on cadmium concentration in small mammals, *J. Environ. Qual*., 31, 188, 2002.
75. Dodds–Smith, M.E., Johnson, M.S., and Thompson, D.J., Trace metal accumulation by the shrew *Sorex araneus*. III. Tissue distribution in kidney and liver, *Ecotox. Environ. Safety*, 24, 118, 1992.
76. Hunter, B.A., Johnson, M.S., and Thompson, D.J., Ecotoxicology of copper and cadmium in a contaminated grassland ecosystem: tissue distribution and age accumulation in small mammals, *J. App. Ecol*., 26, 89, 1989.
77. Ma, W., Methodological principles of using small mammals for ecological hazard assessment of chemical soil pollution, with examples on cadmium and lead, in *Ecotoxicology of Soil Organisms*, Donker, M.H., Eijackers, H., and Heinbach, F., Eds., SETAC, CRC Press, Boca Raton, FL, 1994, 357.
78. Pedersen, H.C. and Myklebust, I., Age-dependent accumulation of cadmium and zinc in the liver and kidneys of Norwegian willow ptarmigan, *Bull. Environ. Contam. Toxicol*., 51, 381, 1993.
79. Froslie, A., Haugen, A., Holt, G., and Norheim, G., Levels of cadmium in liver and kidneys from Norwegian cervides, *Bull. Environ. Contam. Toxicol*., 37, 453, 1986.
80. Milton, A., Johnson, M.S., and Cooke, J.A., Lead within ecosystems on metalliferous mine tailings in Wales and Ireland, *Sci. Total Environ*., 299, 177, 2002.
81. Vega, M.M., Solorzano, J.C., Medina, A.A., Luna, C.H., and Salvinus, J.V.C., Lead: intestinal absorption and mobilisation during lactation, *Human Exp. Toxicol*., 15, 872, 1996.
82. Jefferies, D.J. and French, M.C., Lead concentration in small mammals trapped on roadside verges and field sites, *Environ. Pollut*., 3, 147, 1972.
83. Lock, K. and Janssen, C.R., Zinc and cadmium body burdens in terrestrial oligochaetes; use and significance in environmental risk assessment, *Environ. Toxicol. Chem*., 20, 2067, 2001.
84. Ma, W., Denneman, W., and Faber, J., Hazardous exposure of ground-living small mammals to cadmium and lead in contaminated terrestrial ecosystems, *Arch. Environ. Contam. Toxicol*., 20, 266, 1991.
85. Milton, A., Cooke, J.A., and Johnson, M.S., Accumulation of lead, zinc, and cadmium in a wild population of *Clethrionomys glareolus* from an abandoned lead mine, *Arch. Environ. Contam. Toxicol*., 44, 405, 2003.
86. Myklebust, I. and Pedersen, H.C., Accumulation and distribution of cadmium in willow ptarmigan, *Ecotoxicology*, 8, 457, 1999.
87. Laurinolli, M. and Bendell–Young L.I., Copper, zinc, and cadmium concentrations in *Peromyscus maniculatus* sampled near an abandoned mine, *Arch. Environ. Contam. Toxicol*., 30, 481, 1996.
88. Stewart, A.K. and Magee, A.C., Effects of zinc toxicity on copper, phosphate and magnesium metabolism in young rats, *J. Nutr.*, 287, 82, 1964.
89. Flick, D.F., Kraybill, H.F., and Dimitroff, J.M., Toxic effects of cadmium: a review, *Environ. Res*., 4, 71, 1971.
90. Powell, G.W., Miller, W.J., Morton, J.D., and Clifton, C.M., Influence of dietary Cd level and supplemental Zn on Cd toxicity in the bovine, *J. Nutr.*, 84, 205, 1964.
91. Scheuhammer, A.M., Influence of reduced dietary calcium on the accumulation of lead, cadmium, and aluminum in birds, *Environ. Pollut*., 94, 337, 1996.
92. Friberg, L., Piscator, M., Nordeberg, G.F., and Kjellstorm, T., *Cadmium in the Environment*, CRC Press, Cleveland, OH, 1974.
93. Suzuki, K.T., Studies of cadmium uptake and metabolism by the kidney, *Environ. Health Perspect*., 54, 21, 1984.
94. Roberts, R.D., and Johnson, M.S., Dispersal of heavy metals from abandoned mine workings and their transference through the terrestrial food chains, *Environ. Pollut*., 16, 293, 1978.
95. Robinson, C.J., Hall, S., and Beshir, S.O., Hormonal modulation of mineral metabolism in reproduction, *Proc. Nutr. Soc*., 42, 169, 1983.
96. Fullmer, C.S., Intestinal calcium and lead absorption: effects of dietary lead and calcium, *Environ. Res*., 54, 159, 1991.

97. Mautino, M., Lead and zinc intoxication in zoological medicine: a review, *Zoo. Wildlife Med.*, 28, 28, 1997.
98. Shore, R.F. and Douben, P.E.T., The ecotoxicological significance of Cd intake and residues in terrestrial small mammals, *Ecotox. Environ. Safety*, 29, 101, 1994.
99. Wlostowski, T.A., Krasowska, A., and Dworakowski, W., Low ambient temperature decreases cadmium accumulation in the liver and kidneys of the bank vole (*Clethrionomys glareolus*), *Biometals*, 9, 363, 1996.
100. Barron, M.G., Bioaccumulation and bioconcentration in aquatic organisms, in *Handbook of Ecotoxicology*, Hoffman, D.J., Rattner, B.A., Burton, G.A., Jr., and Cairns, J., Jr., Eds., Lewis Publishers, Boca Raton, FL, 2003, 877.
101. Suedel, B.C., Boraczek, J.A., Peddicord, R.K., Clifford, P.A., and Dillon, T.M., Trophic transfer and biomagnification potential of contaminants in aquatic ecosystems, *Rev. Environ. Contam. Toxicol.*, 136, 21, 1994.
102. Fisher, N.S. and Wang, W-X., The trophic transfer of silver in marine herbivores: a review of recent studies, *Environ. Toxicol. Chem.*, 17, 562, 1998.
103. Reinfelder, J.R., Fisher, N.S., Luoma, S.N., Nichols, J.W., and Wang, W-X., Trace element trophic transfer in aquatic organisms: a critique of kinetic model approach, *Sci. Total Environ.*, 219, 117, 1998.
104. Chen, C.Y., Stemberger, R.S., Klane, B., Blum, J.D., Pickhardt, P.C., and Folt, C.L., Accumulation of heavy metals in food web components across a gradient of lakes, *Limnol. Oceanogr.*, 45, 1525, 2000.
105. Shi, D. and Wang, W-X., Understanding the differences in Cd and Zn bioaccumulation and subcellular storage among different population of marine clams, *Environ. Sci. Tech.*, 38, 449, 2004.
106. Wang, W.-X. and Fisher, N.S., Delineating metal accumulation pathways for marine invertebrates, *Sci. Total. Environ.*, 237/238, 459, 1999.
107. Wang, W-X. and Fisher, N.S., Accumulation of trace elements in a marine copepod, *Limnol. Oceanogr.*, 43, 273, 1998.
108. Reinfelder, J.R. and Fisher, N.S., Retention of elements absorbed by juvenile fish (*Menidia menidia*, *Menidia beryllina*) from zooplankton prey, *Limnol. Oceanogr.*, 39, 1783, 1994.
109. Fisher, N.S., Teyssie, J.L., Fowler, S.W., and Wang, W-X., The accumulation and retention of metals in mussels from food and water: a comparison under field and laboratory condition, *Environ. Sci. Tech.*, 30, 3232, 1996.
110. Wang, W.-X. and Fisher, N.S., Assimilation efficiencies of chemical contaminants in aquatic invertebrates: a synthesis, *Environ. Toxicol. Chem.*, 18, 2034, 1999.
111. Mason, R.P., Reinfelder, J.R., and Morel, F.M.M., Uptake, toxicity, and trophic transfer of mercury in a coastal diatom, *Environ. Sci. Technol.*, 30, 1835, 1996.
112. Rainbow, P.S., Trace metal concentrations in aquatic invertebrates: why and so what? *Environ. Pollut.*, 120, 497, 2002.
113. Nott, J.A. and Nicolaidou, A., Transfer of metal detoxification along marine food chains, *J. Mar. Biol. Assoc (U.K.)*, 70, 905, 1990.
114. Wallace, W.G. and Lopez, G.R., Relationship between subcellular cadmium distribution in prey and cadmium, *Estuaries*, 19, 923, 1996.
115. Wallace, W.G., Lopez, G.R., and Levington, J.S., Cadmium resistance in an oligochaete and its effect on cadmium trophic transfer to an omnivorous shrimp, *Mar. Ecol. Prog. Ser.*, 172, 225, 1998.
116. Rainbow, P.S., Phylogeny of trace metal accumulation in crustaceans, in *Metal Metabolism in Aquatic Environments*, Langston, W.J. and Bebianno, M., Eds., Chapman & Hall, London, 1998, 285.
117. Rainbow, P.S. and White, S.L., Comparative strategies of heavy metal accumulation by crustaceans: zinc, copper, and cadmium in a decapod, and amphipod and a barnacle, *Hydrobiologia*, 174, 245, 1989.
118. Abdennour, C., Smith, B.D., Boulakoud, M.S., Samraoui, B., and Rainbow, P.S., Trace metals in marine, brackish and freshwater prawns (Crustacea, Deacpoda) from northeast Algeria, *Hydrobiologia*, 432, 217, 2000.
119. Johanson, P., Hansen, M.M., Asmund, G., and Neilsen, P.B., Marine organisms as indicators of heavy metal pollution exposure from 16 years of monitoring at a lead–zinc mine in Greenland, *Chem. Ecol.*, 5, 35, 1991.
120. Ridout, P.S., Willcocks, A.D., Morris, R.J., White, S.L., and Rainbow, P.S., Concentration of Mn, Fe, Cu, Zn and Cd in the mesoplagic decapod *Systellaspis debilis* from the east Atlantic Ocean, *Ocean. Mar. Biol.*, 87, 285, 1985.

121. Paez–Osuma, F. and Ruiz–Fernandez, C., Trace metals in the Mexican shrimp *Peneaus vannamei* from estuarine and marine environments, *Environ. Pollut*., 87, 243, 1995.
122. Rainbow, P.S., Trace metal concentration in a Hong Kong penaid prawn, Metapenaeopsis palmensis (Haswell), in *Proc. 2nd Int. Marine Bio. Workshop: The Marine Flora and Fauna of Hongkong and Southern China*, Morton, B., Ed., Hong Kong University Press, 1986, 1221.
123. Rainbow, P.S., Heavy metals in invertebrates, in *Heavy Metals in Marine Environment*, Furness, R.W., and Rainbow, P.S., Eds., CRC Press, Boca Raton, FL, 1990, 67.
124. Wetzel, R.G., *Limnology: Lake and River Ecosystems*, 3rd ed., Academic Press, San Diego, CA, 2001, 396.
125. Bryan, G.W. and Langston, W.S., Bioavailability, accumulation and effects of heavy metals in sediments with special reference to United Kingdom estuaries: a review, *Environ. Pollut.* 79, 89, 1992.
126. Morales–Hernandez, F., Soto–Jimnez, M.F., and Paez–Osuna, F., Heavy metals in sediments and lobster (*Panulirus gracilis*) from the discharge area of the submarine sewage outfall in Mazatlan Bay (SE Gulf of California), *Arch. Environ. Contam. Toxicol*., 46, 485, 2004.
127. Tessier, A. and Campbell, P.G.C., Partitioning of trace metals in sediments: relationships with bioavailability, *Hydrobiologia*, 149, 43, 1987.
128. Watling, L., The sedimentary milieu and its consequences for resident organisms, *Am. Zool*., 31, 789, 1991.
129. Knezovich, J.P., Harrison, F.L., and Wilhelm, R.G., The bioavailability of sediment-sorbed organic chemicals: a review, *Water Air Soil Pollut*., 32, 233, 1987.
130. Schrap, S.M., Bioavailability of organic chemicals in aquatic environments, *Comp. Biochem. Physiol*., 100C, 13, 1991.
131. Smith, D.S., Bell, R.A., and Kramer, J.R., Metal speciation in natural waters with emphasis on reduced sulfur groups as strong metal binding sites, *Comp. Biochem. Physiol. C*, 133, 65, 2002.
132. Brown, P.L. and Markich, S.J., Evaluation of the free ion activity model of metal–organisms interaction: extension of the conceptual model, *Aquat. Toxicol*., 51, 177, 2000.
133. Hodson, P.V., The effect of metal metabolism on uptake, disposition and toxicity in fish, *Aquat. Toxicol*., 11, 3, 1988.
134. Barron, M.G. and Albeke, S., Calcium control of zinc uptake in rainbow trout, *Aquat. Toxicol*., 50, 257, 2000.
135. Burger, J., Gaines, K.F., Boring, C.S., Stephens, W.L., Snodgrass, J., Dixon, C., McMohan, M., Shukla, S., Shukla, T., and Gochfeld, M., Metal levels in fish from the Savannah River: potential hazards to fish and other receptors, *Environ. Res A*., 89, 85, 2002.
136. Langston, W.J. and Spence, S.K., Biological factors involved in metal concentrations observed in aquatic organisms, in *Metal Speciation and Bioavailability in Aquatic Systems*, Tessier, A. and Turner, D.R., Eds., John Wiley & Sons, New York, 1995, 407.
137. Campbell, K.R., Concentrations of heavy metal associated with urban runoff in fish living in stormwater treatment ponds, *Arch. Environ. Contam. Toxicol*., 27, 352, 1994.
138. Chen, C.Y. and Folt, C.L., Bioaccumulation and dimunition of arsenic and lead in a fresh water food web, *Environ. Sci. Tech*., 37, 3878, 2000.
139. Lemly, D.A., Guidelines for evaluating selenium data from aquatic monitoring and assessment studies, *Environ. Monit. Assess*., 28, 83, 1993.
140. Lemly, D.A., Metabolic stress during winter increases the toxicity of selenium to fish, *Aquat. Toxicol*., 27, 133, 1993.
141. Barron, M.G., Bioaccumulation and bioconcentration in aquatic organisms, in *Handbook of Ecotoxicology*, Hoffman, D.J., Rattner, B.A., Burton, G.A., Jr., and Cairns, J., Jr., Eds., Lewis Publishers, Boca Raton, FL, 1995, 652.
142. Sydeman, W.J. and Jarman, W.M., Trace metals in seabirds, stellar sea lion, and forage fish and zooplankton from central California, *Mar. Pollut. Bull*., 36, 828, 1998.
143. Phillips, G.R., Lenhart, T.E., and Gregory, R.W., Relations between trophic position and mercury accumulation among fishes from the Tongue River Reservoir, Montana, *Environ. Res*., 22, 73, 1980.
144. Tayel, F.T.R. and Shriadah, M.M.A., Fe, Cu, Mn, Pb, and Cd in some fish species from western harbor of Alexandria, Egypt, *Bull. Natl. Inst. Oceanogr. Fish*., 22, 85, 1996.

145. Villar, C., Stripeikis, J., Colautti, D., D'Huicque, L., Tudino, M., and Bonetto, C., Metal contents in two fishes of different feeding behavior in lower Parana River and Rio de la Plata Estuary, *Hydrobiologia*, 457, 225, 2001.
146. Lange, T.R., Royals, H.E., and Connor, L.L., Mercury accumulation in largemouth bass (*Micropterus salmoides*) in a Florida lake, *Arch. Environ. Contam. Toxicol*., 27, 466, 1994.
147. Stewart, A.R., Luoma, S.N., Schlekat, C.E., Doblin, M.A. and Hieb, K.A, Food web pathway determines how selenium affects aquatic ecosystems: a San Francisco Bay case study, *Environ. Sci. Tech*., 38, 4519, 2004.
148. Besser, J.M., Brumbaugh, W.G., May, T.W., Church, S.E., and Kimball, B.A., Bioavailability of metals in stream food webs and hazards to brook trout (*Salvelinus fontinalis*) in the upper Animas River watershed, Colarado, *Arch. Environ. Contam. Toxicol*., 40, 48, 2001.
149. Moore, J.W., Luoma, S.N., and Peters, D., Downstream effects of mine effluent on an intermontane riparian system, *Can. J. Fish Aquat. Sci*., 48, 222, 1991.
150. Clements, W.H. and Kiffney, P.M., Integrated laboratory and field approach for assessing impacts of heavy metals at the Arkansas River, Colorado, *Environ. Toxicol. Chem*., 13, 397, 1994.
151. Kay, S.H., Cadmium in aquatic food webs, *Res. Rev*., 96, 13, 1985.
152. Handy, R.D., Dietary exposure to toxic metals in fish, in *Toxicology of Aquatic Pollution*, Taylor, E.W., Ed., University Press, Cambridge, 1996, 29.
153. Castilhos, Z.C. and Bidone, E.D., Hg biomagnification in ichthyofauna of the Tapajos River region, Amazonia, *Bull. Environ. Contam. Toxicol*., 64, 693, 2000.
154. Yost, K.J., Miles, L.J., and Parsons, T.W., A method for estimating dietary intake of environmental trace contaminants: cadmium-a case study, *Environ. Int*., 3, 473, 1980.
155. Kjellstrom, T., Lind, B., Linnman, L., and Elinder, C., Variation in Cd concentration in Swedish wheat and barley, *Arch. Environ. Health*, 30, 321, 1975.
156. Jones, K.C., Jackson, A., and Johnston, A.E., Evidence for an increase in the Cd content of herbage since the 1860s, *Environ. Sci. Technol*., 834, 26, 1992.
157. Wagner, G.J., Accumulation of cadmium in crop plants and its consequences to human health, *Adv. Agron*., 51, 173, 1993.
158. Ryan, J.A., Pahren, H.R., and Lucas, J.B., Controlling cadmium in the human chain: review and rational based on health effects, *Environ. Res*., 28, 251, 1982.
159. McLaughlin, M.J., Parker, D.R., and Clarke, J.M., Metals and micronutrients — food safety issues, *Field Crops Res*., 60, 143, 1999.
160. Satarug, S., Haswell–Elkins, M.R., and Moore, M.R., Safe levels of cadmium intake to prevent renal toxicity in human subjects, *Br. J. Nutr*., 84, 791, 2000.
161. van Bruwaene, R., Kirchmann, R., and Impens, R., Cadmium contamination in agriculture and zoo technology, *Experentia*, 40, 43, 1984.
162. Honda, R., Tawara, K., Nishijo, M., Nakegawa, H., Tanebe, K., and Saito, S., Cadmium exposure and trace elements in human breast milk, *Toxicology*, 186, 255, 2003.
163. Frkovic, A., Kras, M., and Alebic–Juretic, A., Lead and cadmium content in human milk from northern Adriatic area of Croatia, *Bull. Environ. Contam. Toxicol*., 58, 16, 1999.
164. Sonawane, B.R., Chemical contaminants in human milk: an overview, *Environ. Health Perspect*., 103, 197, 1995.
165. Sherlock, J.C., Cadmium in foods and diet, *Experientia*, 40, 152, 1984.
166. Walker, R. and Herrman, J.L., Summary and conclusions of the joint FAO/WHO Expert Committee on Food Additives, Report 55, World Health Organization, Geneva, 2000.
167. Reeves, P.G. and Vanderpool, R.A., Cadmium burden of men and women who report regular consumption of confectionary sunflower kernels containing a natural abundance of Cd, *Environ. Health Perspect*., 105, 1098, 1997.
168. Dorea, J.G., Mecury and lead during breast feeding, *Br. J. Nutr*., 92, 21, 2004.
169. Jensen, S. and Jernelov, A., Biological methylation of mercury in aquatic organisms, *Nature*, 223, 753, 1969.
170. Clarkson, T.W., Mercury: major issues in environmental health, *Environ. Health Perspect*., 100, 31, 1993.

171. Francesconi, K.A. and Lenanton, R.C.J., Mercury contamination in a semienclosed marine embayment: organic and inorganic mercury content of biota, and factors influencing mercury levels in fish, *Mar. Environ. Res*., 33, 189, 1992.
172. MacCrimmon, H.R., Wren, C.D., and Gots, B.L., Mercury uptake by lake trout, *Salvelinus namaycush*, relative to age, growth, and diet in Tadenac Lake with comparative data from other Precambrian shield lakes, *Can. J. Fish Aquat. Sci*., 40, 114, 1983.
173. Cabana, G., Trembley, A., Klaff, J., and Rasmussen, J.B., Pelagic food chain structure in Ontario lakes: a determinant of mercury levels in lake trout (*Salvelinus namaycush*), *Can. J. Fish Aquat. Sci*., 51, 381, 1994.
174. Lange, T.R., Royals, H.E., and Connor, L.L., Influence of water chemistry on mercury concentration in large mouth bass from Florida lakes, *Trans. Am. Fish Soc*., 74, 122, 1993.
175. Burger, J., Dixon, C., Boring, C.S., and Gochfeld, M., Effects of deep frying fish on risk from mercury, *J. Toxicol. Environ. Health, Part A*, 66, 817, 2003.
176. Morgan, J., Berry, M.R., and Graves, R.L., Effects of commonly used cooking practices on total mercury concentration in fish and their impact on exposure assessments, *J. Exposure Anal. Environ. Epidemiol*., 7, 119, 1997.
177. Mahaffey, K.R., Methyl mercury exposure and neurotoxicity, *J. Am. Med. Assoc*., 280, 737, 1998.
178. Barbosa, A.C. and Dorea J.G., Indices of mercury contamination during breast feeding in the Amazon basin, *Environ. Toxicol. Pharmacol*., 6, 71, 1998.
179. Drexler, H. and Schaller, K.H., The mercury concentration in breast milk resulting from amalgam fillings and dietary habits, *Environ. Res*., 77, 124, 1998.
180. WHO, Mercury, IPCS, *Environmental Health Criteria 1*, World Health Organization, Geneva, 1976, 131.
181. Inskip, M.J., and Piotrowski, J.K., Review of the health effects of methylmercury, *J. Appl. Toxicol*., 5, 113, 1985.
182. Wiersma, D., van Goor, B.J., and van der Veen, N.G., Cadmium, lead, mercury and arsenic concentrations in crops and corresponding soils in the Netherlands, *J. Agric. Food Chem*., 34, 1067, 1986.
183. Bakir, F., Dalmuji, S., Amin–Zaki, L., Murtadha, L., Khalidi, A., Al-Rawi, N., Tikriti, S., Dhakir, H., Clarkson, T.W., Smith, J., and Doherty, R., Methylmercury poisoning in Iraq. An interuniversity report, *Science*, 181, 230, 1973.
184. Wade, M.J., Davis, B.K., Carlisle, J.S., Klien, A.K., and Valoppi, L.M., Environmental transformation of toxic metals, *Occup. Med*., 8, 574, 1993.
185. Elliot, H.A., Liberali, M.R., and Huang, C.P, Competitive absorption of heavy metals by soils, *J. Environ. Qual*., 15, 214, 1986.
186. Needleman, H.L. and Bellinger, D., The health effects of low level exposure to lead, *Ann. Rev. Public Health*, 12, 111, 1991.
187. Mendola, P., Selevan, S.G., Gutter, S., and Rice, D., Environmental factors associated with a spectrum of neurodevelopmental deficits, *Ment. Retard. Dev. Disability Res. Rev*., 8, 188, 2002.
188. WHO, Minor and trace elements in human milk, *Report of a Joint WHO/IEAE Collaborative Study*, World Health Organization, Geneva, 1989.
189. Chamberlain, A.C., Prediction of response of blood lead to airborne and dietary lead from volunteer experiments with lead isotopes, *Proc. R. Soc. Lond*., 224B, 149, 1985.
190. Silbergeld, E.K., Lead in bone: implications for toxicology during pregnancy and lactation, *Environ. Health Perspect*., 91, 63, 1991.
191. O'Neill, P., Arsenic, in *Heavy Metals in Soils*, Alloway, B.J., Ed., John Wiley & Sons, New York, 1990, 83.
192. Hughes, M.F., Arsenic toxicity and potential mechanism of action, *Toxicol. Lett*., 133, 1, 2002.
193. NRC, *Arsenic in Drinking Water*, Goyer, R.A., Contor, K.P., Eaton, D.L., Henderson, R.F., Kosnett, M.J., Ryan, L.M., Thompson, K.M., Vahter, M.E., and Walker, B., Jr., Subcommittee on arsenic in drinking water, National Research Council, National Academy of Sciences, National Academy Press, Washington, D.C. 2001.
194. Suner, M.A., Deseva, V., Munoz, O., Lopez, F., Montoro, R., Aeias, A.M., and Blanco, J., Total and inorganic arsenic in fauna of the Guadalquivir Estuary: environmental and human health implications, *Sci. Total Environ*., 242, 261, 1999.

195. Falconer, C.R., Shepherd, R.J., Pirie, J.M., and Topping, G., Arsenic levels in fish and shellfish from the North Sea, *Exp. Mar. Biol. Ecol*., 71, 193, 1983.
196. Lewis, R., Metals, in *Occupational and Environmental Medicine*, LaDou, J., Ed., McGraw–Hill, New York, 1997, 405.
197. Gochfeld, M., Factors influencing susceptibility to metals, *Environ. Health Perspect*., 105 (suppl. 4), 817, 1997.
198. Waisberg, M., Joseph, P., Hale, B., and Beyersmann, D., Molecular and cellular mechanisms of cadmium carcinogenesis, *Toxicology*, 192, 95, 2003.
199. Nogawa, K., Kido, T., Yamada, Y., Tsuritani, I., Honda,R., Ishizaki, M., and Terahata, K., α_1-microglobulin in urine as an indicator of renal tubular damage caused by environmental cadmium exposure, *Toxicol. Lett*., 22, 63, 1984.
200. Horiguchi, H., Teranishi, H., Niiya, K., Aoshima, K., Katoh, T., Sakuragawa, N., and Kasuya, M., Hypoproduction of erythropoieten contributes to anemia in chronic cadmium intoxication: clinical study on Itai-Itai disease in Japan, *Arch. Toxicol*.,68, 632, 1994.
201. Horiguchi, H., Sato, M., Konno, N., and Fukushima, M., Long-term cadmium exposure induces anemia in rats through hypoproduction of erythropoietin in kidneys, *Arch. Toxicol*., 71, 11, 1996.
202. Aoshima, K., Fan, J., Cai, Y., Katoh, T., Teranishi, H., and Kasuya, M., Assessment of bone metabolism in cadmium-induced renal tubular dysfunction by measurement of biochemical markers, *Toxicol. Lett*., 136, 183, 2003.
203. Goyer, R.A., Epstein, S., Bhattacharya, M., Korach, K.S., and Pounds, J., Environmental risk factors for osteoporosis, *Environ. Health Perspect*., 102, 390, 1994.
204. Buchet, J.P., Lauwerys, R., Roels, H., Brenard, A., Bruaux, P., Claeys, F., Ducoffre, G., DePlaen, P., Staessen, J., Amery, A., Lijnen, P., Thijs, L., Rondia, D., Sartor, F., Saint Remy, A., and Nick, L., Renal effects of cadmium body burden of the general population, *Lancet*, 336, 699, 1990.
205. Hellstorm, L., Elinder, C.G., Dahlberg, B., Lundberg, M., Jarup, L., Persson, B., and Axelson, O., Cadmium exposure and end-stage renal disease, *Am. J. Kidney Dis*., 38, 1001, 2001.
206. Hallenback, W.H., Human health effects of exposure to cadmium, *Experientia*, 70, 136, 1984.
207. Alfven, T., Elinder, C.G., Carlesson, M.D., Grubb, A., Hellstorm, L., Persson, B., Petersson, C., Spang, G., Schutz, A., and Jarup, L., Low-level cadmium exposure and osteoporosis, *J. Bone Miner. Res*., 15, 1579, 2000.
208. Honda, R., Tsuritani, I., Ishida, M., Noborisaka, Y., and Yamada, Y., Relationship between ultrasonic calcaneal bone measurements and urinary cadmium excretion in women living in non-Cd-polluted area, *J. Bone Miner. Res*., 12 (suppl 1), S1, 1997.
209. Blakley, B.R. and Rajpal, S.T., The effect of cadmium on antibody responses to antigens with different cellular requirements, *Int. J. Immunopharmacol*., 8(8), 1009, 1986.
210. Babich, H. and Davis, D.L., Food tolerances and action levels: do they adequately protect children? *Bioscience*, 31, 429, 1981.
211. Spivey Fox, M.R., Nutritional factors that may influence bioavailability of Cd, *J. Environ. Qual*., 17, 175, 1988.
212. IARC, Cadmium and cadmium compounds, in *Beryllium, Cadmium, Mercury and Exposure in the Glass Manufacturing Industry, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. 58, International Agency for Research on Cancer, Lyon, 1993, 119.
213. WHO, Methylmercury, *Environmental Health Criteria*, vol. 101, World Health Organization, Geneva, 1990.
214. Dixon, R. and Jones, B., Mercury concentrations in stomach contents and muscle of five species from northeast coast of England, *Mar. Pollut. Bull*., 28, 741, 1994.
215. Kerper, L.E., Ballatori, N., and Clarkson, T.W., Methylmercury transport across the blood–brain barrier by an amino acid carrier, *Am. J. Physiol*., 262, R761, 1992.
216. Castoldi, A.F., Coccini, T., Ceccatelli, S., and Manzo, L., Neurotoxicity and molecular effects of methylmercury, *Brain Res. Bull*., 55, 197, 2001.
217. Amin–Zaki, L., Elhassani, S., Majeed, M.A., Clarkson, T.W., Doherty, R.A., and Greenwood, M., Intrauterine methyl mercury poisoning in Iraq, *Pediatrics*, 54, 587, 1974.
218. Magos, L., Peristianis, G.C., Clarkson, T.W., Brown, A., Preston, S., and Snowden, R.T., Comparative study of sensitivity of male and female rats to methylmercury, *Arch. Toxicol*., 48, 11, 1981.

219. Grandjean, P., Weihe, P., White, R.F., and Debes, F., Cognitive performance of children prenatally exposed to "safe" levels of methyl mercury, *Environ. Res. A*., 77, 165, 1998.
220. Gimenez–Llort, E., Ahlbom, E., Dare, E., Vahter, M., Ogren, S.-O., and Ceccateeli, S., Prenatal exposure to methylmercury changes dopamine-modulated motor activity during early ontogeny: age and gender effects, *Environ. Toxicol. Pharmacol*., 9, 61, 2001.
221. Sakamoto, M., Nakano, A., and Akagi, H., Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution, *Environ. Res*., 87, 92, 2001.
222. Costa, M., Zhitkovich, A., Gargas, M., Pautenbach, D., Finley, B., Kuykendau, J., Billing, R., Clarkson, T.J., Wettehahn, J., Xu, J., Patierno, S., and Bogdanffy, M., Interlaboratory validation of a new assay for DNA–protein crosslinks, *Mut. Res*., 369, 13, 1996.
223. IARC, Mercury, in beryllium, cadmium, *Beryllium, Cadmium, Mercury and Exposure in the Glass Manufacturing Industry, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. 58, International Agency for Research on Cancer, Lyon, 1993, 119.
224. WHO, Environmental health criteria 165: inorganic lead, World Health Organization, Geneva, 1995.
225. NEPI, Assessing the bioavailability of metals in soil for use in human health risk assessments, Bioavailability Policy Project Phase II: Metals Task Force Report, National Environmental Policy Institute, Washington, D.C., 2000.
226. Goyer, R.A., Lead toxicity: current concerns, *Environ. Health Perspect*. 100, 177, 1993.
227. Goldsein, G.W., Lead poisoning and brain cell function, *Environ. Health Perspect*., 89, 91, 1990.
228. Mortada, W.I., Sobh, M.A., El-Defrawy, M.M., and Farahat, S.E., Study of lead exposure from automobile exhaust as a risk for nephrotocixity among traffic policemen, *Am. J. Nephrol*., 21, 274, 2001.
229. Buchet, J.P., Roels, H., Bernard, A., and Lauwerys, R., Assessment of renal function of workers exposed to inorganic lead, cadmium or mercury vapor, *J. Occup. Med*., 22, 741, 1980.
230. Goyer, R.A. and Rhyne, B.C., Pathological effects of lead, *Int. Rev. Exp. Pathol*. 12, 1, 1973.
231. Gurer, H. and Ercal, N., Can antioxidants be beneficial in the treatment of lead poisoning? *Free Radic. Biol. Med*., 29, 927, 2000.
232. Pounds, J.G., Long, G.J., and Rosen, J.F., Cellular and molecular toxicity of lead in bone, *Environ. Health Perspect*., 91,17, 1991.
233. Gulson, B.L., Mahaffey, K.R., Vidal, M., Jameson, C.W., Lew, A.J., Mizon, K.J., Smith, A.J., and Korsch, M.J., Dietary lead intake for mother/child pairs and relevance to pharmokinetic models, *Environ. Health Perspect*., 105, 1334, 1997.
234. Gulson, B.L., Jameson, C.W., Mahaffey, K.R., Mizon, K.J., Patison, N., Law, A.J., Korsch, M.J., and Salter, M.A., Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother, *Environ. Health Perspect*., 106, 667, 1998.
235. Rossouw, J., Offermeier, J., and van Rooyen, J.M., Apparent central neurotransmitter receptor changes induced by low-level lead exposure during different development phases in the rat, *Toxicol. Appl. Pharmacol*., 91, 132, 1987.
236. Lidsky, T.I. and Scheider, J.S., Lead neurotoxicity in children: basic mechanism and clinical correlates, *Brain*, 126, 5, 2003.
237. Leonard, A. and Lauwerys, R.R., Carcinogenicity, teratogenicity and mutagenicity of arsenic, *Mut. Res./Rev. Genetic. Toxicol*., 75, 49, 1980.
238. Lynn, S., Gurr, J.R., Lai, H.T., and Jan, K.Y., NADH oxidase activation is involved in arsenite-induced oxidative DNA damage in human vascular smooth muscle cells, *Circ. Res*., 86, 514, 2000.
239. Ramos, O., Carrizales, L., Yanez, L., Mejia, J., Batres, L., Ortiz, D., and Diaz–Barriga, F., Arsenic increased lipid peroxidation in rat tissues by a mechanism independent of glutathione levels, *Environ. Health Perspect*., 103 (suppl. 1), 85, 1995.
240. Hartmann, A. and Speit, G., Effect of arsenic and cadmium on the persistence of mutagen-induced DNA lesions in human cells, *Environ. Mol. Mutagen*., 27, 98, 1996.
241. Hartwig, A., Groblinghoff, U.D., Beyersmann, D., Natrajan, A.T., Filon, R., and Mullenders, L.H., Interaction of arsenic(III) with nucleotide excision repair in UV-irradiated human fibroblasts, *Carcinogenesis*, 18, 399, 1997.
242. Wiencke, J.K., Yager, J.W., Varkonyi, A., Hultner, M., and Lutze, L.H., Study of arsenic mutagenesis using the plasmid shuttle vector pZ189 propagated in DNA repair proficient human cells, *Mut. Res*., 386, 335, 1997.

243. Feng, Z., Xia, Y., Tian, D., Wo, K., Schmitt, M., Kwok, R.K., and Mumford, J.L., DNA damage in buccal epithelial cells from individuals chronically exposed to arsenic via drinking water in Inner Mongolia, China, *Anticancer Res*., 21(1A), 51, 2001.
244. HopenhaynRich, C., Biggs, M., Fuchs, A., Bergoglio, R., Tello, E., Nicolli, H., and Smith, A., Bladder cancer mortality associated with arsenic in drinking water in Argentina, *Epidemiology*, 7, 117, 1996.
245. Wolnik, K.A., Fricke, F.L., Capar, S.G., Meyer, M.W., Satzger, R.D., Bonnin, E., and Gaston, C.M., Elements in major raw agricultural crops in the United States. 3. Cadmium, lead and 11 other elements in carrots, field corn, onions, rice, spinach and tomatoes, *J. Agri. Food Chem*., 33, 807, 1985.