Contribution to Medical Geology Book

The Natural Environment - Selenium Deficiency and Toxicity – Process Related Diseases

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Glossary

Alkali Disease:	Can affect animals ingesting feed with a high selenium content and is characterized by dullness, lack of vitality, emaciation, rough coat, sloughing of the hooves, erosion of the joints and bones, anemia, lameness, liver cirrhosis and reduced reproductive performance.
Apoptosis:	Programmed cell death.
Blind Staggers:	Blind staggers occurs in cattle and sheep ingesting high concentrations of selenium and is characterized by impaired vision leading to blindness, anorexia, weakened legs, paralyzed tongue, labored respiration, abdominal pain, emaciation and death.
Crust:	The outermost solid layer of a planet or moon.
Cytochrome P_{450}:	Iron-containing proteins important in cell respiration as catalysts of oxidation-reduction reactions.
Exudative Diathesis:	Selenium deficiency in birds can cause this condition; it is characterized by massive hemorrhages beneath the skin as a result of abnormal permeability of the capillary walls and accumulation of fluid throughout the body.

Glutathione Peroxidase:	A detoxifying enzyme in humans and animals that eliminates hydrogen peroxide and organic peroxides, it has a selenocysteine residue in its active site.
Homeostatic Control:	The ability or tendency of an organism or cell to maintain internal equilibrium by adjusting its physiological processes.
Igneous Rocks:	Formed from the cooling and solidification of molten rock originating from below the Earth's surface, includes volcanic rocks.
Iodothyronine deiodinase:	Selenoproteins responsible for the production and regulation of the active thyroid hormone from thyroxine.
Kashin-Beck Disease:	An endemic osteoarthropathy (stunting of feet and hands) causing deformity of the affected joints, occurs in Siberia, China and North Korea.
Keshan Disease:	An endemic cardiomyopathy (heart disease) that mainly affects children and women of childbearing age in China.

Metamorphic Rocks:	Formed from the alteration of existing rock material due to heat and/or pressure.
Phytotoxicity:	Toxic to plants.
Sedimentary Rocks:	Formed by compression of material derived from the weathering or deposition of eroded rock fragments, marine or other organic debris or chemical precipitates from over-saturated solutions.
Selenocysteine:	An unusual amino acid of proteins, the selenium analogue of cysteine, in which a selenium atom replaces sulfur.
Selenomethionine:	2-amino-4- (methylseleno) butanoic acid.
Selenosis:	Selenium toxicity.
Triiodothyronine:	Also referred to as 3:5,3' triiodothyronine (T_3) produced in the thyroid gland and involved in controlling the rate of metabolic processes in the body and physical development.
Thyroxine:	Also referred to as 3:5,3':5' tetraiodothyronine (T_4) is the major hormone secreted by the thyroid gland. T_4 is

	involved in controlling the rate of metabolic processes in the body and influencing physical development.
Vadose Zone:	Also known as the ‘unsaturated zone’ is the part of the Earth’s surface extending down to the water table.
White Muscle Disease:	This is a complex condition, which is multi-factorial in origin but linked to selenium deficiency and causes degeneration of the muscles in a host of animal species. In lambs born with the disease, death can result after a few days. Later in life, animals have a stiff and stilted gait, arched back are not inclined to move about, lose condition, become prostrate and die.

I. Summary

Selenium (Se) is a naturally occurring metalloid element, which is essential to human and other animal health in trace amounts but is harmful in excess. Of all the elements, selenium has one of the narrowest ranges between dietary deficiency ($< 40\ \mu g\ day^{-1}$) and toxic levels ($> 400\ \mu g\ day^{-1}$) making it necessary to carefully control intakes by humans and other animals hence the importance of understanding the relationships between environmental exposure and health. Geology exerts a fundamental control on the concentrations of selenium in the soils on which we grow the crops and animals that form the human food chain and the selenium status of populations, animals and

crops vary markedly around the world as a result of different geological conditions. Since diet is the most important source of selenium in humans, understanding the biogeochemical controls on the distribution and mobility of environmental selenium is key to the assessment of selenium-related health risks. High selenium concentrations are associated with some phosphatic rocks, organic-rich black shales, coals and sulfide mineralization whereas most other rock types contain very low concentrations and selenium deficient environments are far more widespread than seleniferous ones. However, health outcomes are not only dependent on the total selenium content of rocks and soils but also on the amount of selenium taken up into plants and animals, the bioavailable selenium. This chapter demonstrates that even soils containing adequate total amounts of selenium can still produce selenium-deficient crops if the selenium is not in a form ready for plant uptake.

The links between the environmental biogeochemistry of selenium and health outcomes have been documented for many years. The element was first identified in 1817 by the Swedish chemist Jons Jakob Berzelius, however, selenium toxicity problems in livestock had been recorded for hundreds of years previously although the cause was unknown. Marco Polo reported a hoof disease in horses during travels in China in the 13th century and similar problems were noted in livestock in Colombia in 1560 and in South Dakota (USA) in the mid-19th century where the symptoms were termed ‘alkali disease’*. In 1931, this disease, which is characterized by hair and hoof loss and poor productivity, was identified as selenium toxicosis (selenosis*). Since then, seleniferous areas have been reported in Ireland, Israel, Australia, Russia, Venezuela, China, USA and South Africa.

Conversely, selenium was identified as an essential trace element during pioneering work into selenium-responsive diseases in animals in the late 1950s and early 1960s. Selenium forms a vital constituent of the biologically important enzyme glutathione peroxidase* (GSH-Px), which acts as an anti-oxidant preventing oxidative cell degeneration. In animals, selenium deficiency has been linked to muscular weakness and muscular dystrophy but also causes reduced appetite, poor growth and reproductive capacity and embryonic deformities. These disorders are generally described as 'white muscle disease'* (WMD). Following these discoveries, selenium deficiencies in crops and livestock have been reported in all regions of the world including the USA, UK, Finland, Denmark, Sri Lanka, New Zealand, Australia, India, Canada, Thailand, Africa and China and selenium supplementation has become common practice in agriculture.

Selenium deficiency has also been implicated in the incidence of a heart disorder (Keshan disease*) and bone and joint condition (Kashin-Beck disease*) in humans in various parts of China. Recent research has shown that selenium deficiency also adversely affects thyroid hormone metabolism, which is detrimental to growth and development. Indeed, approximately 20 essential selenoproteins have now been identified in microbes, animals and humans, many of which are involved in catalytic functions in the body and selenium deficiency has been implicated in a host of conditions including cancer, heart disease, immune system function and reproduction. This chapter outlines some of the health problems in humans and animals that can arise as a result of selenium deficiency and toxicity in the natural environment. These links are more obvious in regions of the world where the population is dependent on local foodstuffs in the diet but studies show that even in countries such as the USA where food is derived from range of exotic sources, the local environment still determines the selenium status of the population, a fact which should not be ignored since medical science continues to discover new essential functions for this biologically important element.

II Selenium in the Environment

The naturally occurring element selenium belongs to group VIA of the periodic table and has chemical and physical properties that are intermediate between metals and non-metals (Table 1). Selenium occurs in nature as six stable isotopes, however, it should be noted that although ^{82}Se is generally regarded as a stable isotope it is actually a β^- emitter with a very long half-life of 1.4×10^{20} yr. The chemical behavior of selenium resembles that of sulfur and like sulfur, selenium can exist in the 2^-, 0, 4^+ and 6^+ oxidation states (Table 2). As a result of this complex chemistry, selenium is found in all natural materials on Earth including rocks, soils, waters, air and plant and animal tissues (Table 3).

At the global scale, selenium is constantly recycled in the environment via the atmospheric, marine and terrestrial systems. Estimates of selenium flux indicate that anthropogenic activity is a major source of selenium release in the cycle, whereas the marine system constitutes the main natural pathway (Table 4) (Haygarth, 1994). Selenium cycling through the atmosphere is significant because of the rapidity of transport but the terrestrial system is most important in terms of animal and human health because of the direct links with agricultural activities and the food chain.

Although the element is derived from both natural and man-made sources, an understanding of the links between environmental geochemistry and health is particularly important for selenium as rocks are the primary source of the element in the terrestrial system (Table 5) (Neal, 1995; Fleming, 1980). Selenium is dispersed from the rocks through the food chain via complex biogeochemical cycling processes including weathering to form soils, rock-water interactions and biological activity (Figure 1). As a result, selenium is not distributed evenly across the planet, rather concentrations differ markedly depending on local conditions and an understanding of these variations is essential to aid the amelioration of health problems associated with selenium deficiency and toxicity. The following sections of this chapter provide a brief summary of anthropogenic sources of the element before going on to discuss the important aspects of selenium in the natural biogeochemical cycle and impacts on health.

A. Man-made Sources of Selenium.

Following its discovery in 1817, little industrial application was made of selenium until the early 20th century when it began to be used as a red pigment and improver in glass and ceramic manufacture, however it was not until the invention of the photocopier in the 1930s that demand for the element significantly increased due to its photoelectric and semi-conductor properties. Today selenium is widely used in a number of industries (Table 6), most commonly selenium dioxide is employed as a catalyst in organic synthesis and as an antioxidant in inks, mineral, vegetable and lubricating oils. Selenium mono- and disulfide are also used in anti-dandruff and anti-fungal pharmaceuticals (US-EPA, 2002b; Haygarth, 1994; WHO, 1987).

The world industrial output of selenium was over 2310 tonnes in 1995, the largest producers being Japan, Canada and the USA. In 1985, production of selenium in the USA alone reached 195 tonnes, which was used mainly in the electronic/ photocopying and glass industries (Table 6). It is not economical to mine mineral deposits specifically for selenium, rather the element is recovered from the electrolytic refining of copper and lead and from the sludge accumulated in sulfuric acid plants (US-EPA, 2002a; US-EPA, 2002b).

Selenium compounds are released to the environment during the combustion of coal and petroleum fuels, during the extraction and processing of copper, lead, zinc, uranium and phosphate and during the manufacture of selenium-based products. According to monitoring data in the USA, between 1987 and 1993 over 460 tonnes of selenium were released to the environment, primarily from copper-smelting industries (Table 7) (US-EPA, 2002a; US-EPA, 2002b).

It is estimated that 76 000 – 88 000 tonnes year^{-1} of selenium are released globally from anthropogenic activity, compared to natural releases of 4500 tonnes year^{-1} giving a biospheric enrichment factor value of 17. This value is significantly higher than 1 indicating the important influence of man in the cycling of selenium (Nriagu, 1991). For example, long-term monitoring data from the Rothamstead Agricultural Experimental Station in the UK demonstrate the impact of anthropogenic activity on selenium concentrations in herbage. Samples collected between 1861 and 1990 bulked at 5 year intervals reveal that the highest concentrations occurred between 1940 – 1970 coinciding with the period of intensive coal use. With the move to fuel sources such as nuclear, oil and gas in more recent decades, selenium concentrations in herbage are declining (Haygarth ,1994).

Selenium is also released inadvertently to the environment from the agricultural use of phosphate fertilizers; from the application of sewage sludge and manure to land and from the use of selenium-containing pesticides and fungicides (Table 5). For example, in the European Union it is no longer permissible to dump sewage sludge at sea, consequently the application to land has increased in recent years and to help avoid potential environmental problems, a maximum permissible concentration (MAC) of selenium in sewage sludge in the UK is set at 25 mg kg^{-1} whereas the MAC in soil after application is 3 mg kg^{-1} in the UK and 10 mg kg^{-1} in France. Clearly, the application of sewage sludge to land increases the selenium content of the soil, however, relationships between elevated contents and increased uptake into plants have yet to be established (Haygarth, 1994). The application of selenium-bearing fertilizers to land has been used to remediate selenium deficiency in a number of countries and is discussed in Section V of this Chapter. Environmental problems related to selenium emissions may also arise in areas surrounding selenium processing or fossil fuel burning industries. Selenium concentrations in the air within 0.5 – 10 km of copper-sulfide ore processing plants have been reported to reach 0.15 – 6.5 µg m^{-3} (WHO, 1987).

It is clear that man-made sources of selenium have a major impact upon the selenium cycle, but despite this, the natural environment is still a very important source and pathway of selenium in animal and human exposure and requires careful consideration in selenium-related health studies.

B. Selenium in Rocks.

The most important natural source of selenium in the environment is the rock that makes up the surface of the planet. Selenium is classed as a trace element as average crustal* abundances are generally very low (0.05 - 0.09 mg kg^{-1}, Taylor and McLennan, 1995). Average concentrations in magmatic rocks such as granites rarely exceed these values (Table 3). Relationships with volcanic rocks are more complicated. Volcanoes are a major source of selenium in the environment and it is estimated that over the history of the Earth, volcanic eruptions account for 0.1 g of selenium for every cm^2 of the Earth's surface. Ash and gas associated with volcanic activity can contain significant quantities of selenium and, for example, values of 6 – 15 mg kg^{-1} have been reported in volcanic soils on Hawaii. Conversely, because selenium escapes as high temperature gases during volcanic activity, selenium concentrations left behind in volcanic rocks such as basalts and rhyolites are commonly very low (Jacobs, 1989; Neal, 1995; Fleming 1980; Nriagu, 1989). In general terms, sedimentary rocks* contain greater concentrations of selenium than igneous rocks*, but even so, levels in most limestones and sandstones rarely exceed 0.1 mg kg^{-1} (Neal, 1995). Since these major rock types account for most of the Earth's surface, a picture should begin to emerge that selenium-deficient environments are far more widespread than selenium-adequate or selenium-toxic ones. Exceptions to the generally low concentrations occur in particular types of sedimentary rocks and deposits. Selenium is often associated with the clay fraction in sediments and is found in greater concentrations in rocks such as shales (0.06 mg kg^{-1}) than limestones or sandstones. Very high concentrations ($\leq$ 300 mg kg^{-1}) of selenium have also been reported in some phosphatic rocks, probably reflecting similarities between organically derived PO_4^{3-} and SeO_4^{2-} anions (Jacobs, 1989; Neal, 1995; Fleming 1980; Nriagu, 1989). Selenium concentrations in coal and other organic-rich deposits can be high relative to other rock types and typically range from 1 to 20 mg kg^{-1} (although values of over 600 mg kg^{-1} have been reported in some black shales) with selenium present as organoselenium compounds, chelated species or adsorbed element (Jacobs, 1989). Selenium is often found in sulfide mineral deposits and has been used as a pathfinder for gold and other precious metals in mineral exploration (Boyle, 1979). In most situations, selenium substitutes for sulfur in sulfide minerals due to similarities in crystallography, however, elemental Se^0 is occasionally reported (Neal, 1995; Fleming, 1980; Tokunaga et al., 1996). The main mineral forms and common mineral associations of selenium are outlined in Table 8.

Therefore, the distribution of selenium in the geological environment is highly variable depending on different rock types. An illustration of the relationships between geology and selenium distribution is shown in the map of Wales, UK (Figure 2). Highest selenium in stream sediment concentrations are associated with the mineralized areas of Parys Mountain, the Harlech Dome and Snowdon in north Wales; with the South Wales, Forest of Dean and Pembrokeshire Coalfields and with the Permian Mercia Mudstone Group of the Welsh borderlands. In contrast concentrations over Devonian age sandstones in mid-Wales are extremely low (< 0.4 mg kg^{-1}).

C. Selenium in Soil.

In the majority of circumstances there is a very strong correlation between the concentration of selenium in geological parent materials and the soils derived from them. The selenium content of most soils is very low 0.01 - 2 mg kg^{-1} (world mean 0.4 mg kg^{-1}) but high concentrations of up to 1200 mg kg^{-1} have been reported in some seleniferous areas (Table 9) (Fleming, 1980; Jacobs, 1989; Mayland, 1994; Neal, 1995). The relationships between geology, soil selenium concentrations, uptake into plants and health outcomes in animals were first examined in detail in pioneering work carried out during the 1930s by Moxon (1937). Soils capable of producing selenium-rich vegetation toxic to livestock were reported over black shale and sandstone deposits of the Great Plains of the USA. Subsequent studies into selenium-deficiency-related diseases in animals lead to one of the first maps of the selenium status of soils, vegetation and animals and the establishment of the classic Great Plain seleniferous soil types (Figure 3) (Muth and Allaway, 1963).

Although the underlying geology is the primary control on selenium concentrations in soils, the mobility and uptake of selenium into plants and animals, known as the bioavailability, is determined by a number of bio-physio-chemical parameters. These include the prevailing pH and redox conditions; the chemical form or speciation of selenium; soil texture and mineralogy; organic matter content and the presence of competitive ions. An understanding of these controls is essential to the prediction and remediation of health risks from selenium as, even soils that contain adequate total selenium concentrations can result in selenium deficiency if the element is not in readily bioavailable form.

The principal controls on the chemical form of selenium in soils are the pH and redox conditions (Figure 4). Under most natural redox conditions, selenite (Se^{4+}) and selenate (Se^{6+}) are the predominant inorganic phases with selenite the more stable form. Selenite is adsorbed by ligand exchange onto soil particle surfaces with greater affinity than selenate, this process is pH dependent and adsorption increases with decreasing pH. In acid and neutral soils, selenite forms very insoluble iron oxide and oxyhydroxide complexes such as $Fe_2(OH)_4\ SeO_3$. The low solubility coupled with stronger adsorption makes selenite less bioavailable than selenate. In contrast, selenate, the most common oxidation state in neutral and alkaline soils, is generally soluble, mobile and readily available for plant uptake. For example, experiments have shown that addition of selenate to soils results in ten times more plant uptake than addition of the same amount of selenium as selenite (Jacobs, 1989; Neal, 1995). Elemental selenium(Se^0), selenides (Se^{2-}) and selenium-sulfide salts tend to exist in reducing, acid and organic-rich environments only. The low solubility and oxidation potential of these element species, make them largely unavailable to plants and animals. However, the oxidation and reduction of selenium is closely linked to microbial activity, for example, the bacterium *Bacillus megaterium* is known to oxidize elemental selenium to selenite. It is estimated that perhaps 50% of the selenium in some soils may be in held in organic compounds, however, few have been isolated and identified. To date, selenomethionine* has been extracted from soils and is two to four times more bioavailable to plants than inorganic selenite whereas selenocysteine* is less bioavailable than selenomethionine (Jacobs 1989; Neal, 1995; Mayland, 1994).

The bioavailability of the different selenium species in soils is summarized in Figure 5. In summary, selenate is more mobile, soluble and less well adsorbed than selenite thus selenium is much more bioavailable under oxidizing alkaline conditions and much less bioavailable in reducing acid conditions (Figure 4) (Jacobs, 1989; Neal, 1995; Fleming 1980).

In addition to the speciation of selenium in soils, other soil properties affect mobility. The bioavailability of selenium in soil generally correlates negatively with clay content due to increased adsorption on fine particles, indeed the selenium uptake in plants grown on clay-loamy soils can be half that of plants grown on sandy soils. Iron also exerts a major control on selenium mobility as both elements are affiliated under oxidizing and reducing conditions and adsorption of selenium by iron oxides exceeds that of clay minerals. As mentioned above, the capacity of clays and iron oxides to adsorb selenium is strongly influenced by pH reaching a maximum between pH 3 - 5 and decreasing with increasing pH (Jacobs, 1989; Neal, 1995). Soil organic matter also has a large capacity to remove selenium from soil solution possibly as a result of fixation by organometallic complexes. For example, plant uptake of selenate added to organic-rich soils can be ten times less than from mineral soils (Jacobs, 1989; Neal, 1995).

The presence of ions such as SO_4^{2-} and PO_4^{3-} can influence selenium uptake in plants by competing for fixation sites in the soil and plants. SO_4^{2-} inhibits the uptake of selenium by plants and has a greater effect on selenate than selenite Addition of PO_4^{3-} to soils has been shown to increase selenium uptake by plants as the PO_4^{3-} ion is readily adsorbed in soils and displaces selenite from fixation sites making it more bioavailable. Conversely, increasing the levels of PO_4^{3-} in soils can dilute the selenium content of vegetation by inducing increased plant growth (Jacobs, 1989; Mayland, 1994; Neal, 1995).

Therefore, in any study of the selenium status of soil, consideration of the likely bioavailability is important. Several different chemical techniques are available to assess bioavailability but one of the most widely accepted indicators is the water-soluble selenium content (Jacobs, 1989; Tan, 1989; Fordyce et al., 2000b). In most soils, only a small proportion of the total selenium is dissolved in solution (0.3 – 7%) and water soluble selenium contents are generally < 0.1 mg kg^{-1} (Table 3) (Jacobs, 1989).

The importance of soil selenium bioavailability and health outcomes is exemplified by seleniferous soils in the USA. Toxicity problems in plants and livestock have been reported in soils developed over the Cretaceous shales of the northern mid-West which contain 1 – 10 mg kg^{-1} total selenium because up to 60% of the element is in water-soluble readily bioavailable form in the semi-arid alkaline environment. In contrast, soils in Hawaii with up to 20 mg kg^{-1} total selenium do not cause problems in vegetation and livestock because the element is held in iron and aluminum complexes in the humid lateritic soils of that region (Oldfield, 1999).

D. Selenium in Plants.

Although there is little evidence that selenium is essential for vegetation growth, it is incorporated into the plant structure. Selenium concentrations in plants generally reflect the levels of selenium in the environment such that the same plant species grown over high and low selenium-available soils will contain concentrations reflecting the soil composition. However, an important factor that may determine whether or not selenium-related health problems manifest in animals and humans is the very wide-ranging ability of different plant species to accumulate selenium (Jacobs, 1989; Neil, 1995, WHO, 1987).

Rosenfield and Beath (1964) were the first to classify plants into three groups on the basis of selenium uptake when grown on seleniferous soils. Some examples of this scheme are outlined in Table 10. Selenium accumulator plants grow well on high-selenium soils and can absorb > 1000 mg kg^{-1} of the element, whereas secondary selenium absorbers rarely concentrate more than 50 - 100 mg kg^{-1}. The third group, which includes grains and grasses, usually accumulate less than 50 mg kg^{-1} selenium. Selenium concentration in plants can range from 0.005 mg kg^{-1} in deficient crops to 5500 mg kg^{-1} in selenium accumulators but most plants contain < 10 mg kg^{-1} selenium. Some species of the plant genera *Astragalus*, *Haplopappus* and *Stanleya* are characteristic of seleniferous semi-arid environments in the western USA and other parts of the world and are often used as indicators of high-selenium environments, it should be noted, however, that other species in these genera are non-accumulators (Jacobs, 1989; Neal, 1995; WHO 1987).

The reason why some plants are better at accumulating selenium than others depends upon the selenium metabolism. Plants contain many different selenium compounds and the main form in non-accumulator species is protein-bound selenomethionine, however, selenocysteine, and selenonium have also been reported (Neal, 1995;

Jacobs, 1989). In contrast, the selenium metabolism in accumulator plants is primarily based on water-soluble non-protein forms such as Se-methylselenomethionine. The exclusion of selenium from the proteins of accumulator plants is thought to be the basis of selenium tolerance (Jacobs, 1989; Neal, 1995). Plants also reduce selenate to elemental Se^0 and selenide Se^{2-} forming the volatile organic compounds dimethylselenide and dimethyldiselenide, which are released to the air during respiration giving rise to a 'garlic' odor characteristic of selenium-accumulating plants (Mayland, 1994).

Despite these coping mechanisms, plants can suffer selenium toxicity via the following processes (Jacobs 1989; Fergusson, 1990; Mayland, 1994 and Wu, 1994):

- Selenium competes with essential metabolites for sites in the plant biochemical structure
- Selenium may replace essential ions, mainly the major cations (for example iron, manganese, copper and zinc)
- Selenate can occupy the sites for essential groups such as phosphate and nitrate
- Selenium can be incorporated into analogues of essential sulfur compounds in plant tissues

No phytotoxicity* symptoms have been reported in nature in the USA, but experimental evidence has shown a negative correlation between increased selenium contents in soil and growth (plant dry weight, root length and shoot height all decrease). For example, alfalfa yields have been shown to decline when extractable selenium exceeds 500 mg kg^{-1} in soil. Other symptoms include yellowing, black spots and chlorosis of plant leaves and pink root tissue (Jacobs, 1989 and Wu, 1994). However, phytotoxicity has been reported in nature in China, where high concentrations in soil caused pink discoloration of maize corn-head embryos, the pink color being attributed to the presence of elemental selenium. Levels of >2 mg kg^{-1} and >1.25 mg kg^{-1} selenium were detrimental to the growth and yield of wheat and pea crops respectively (Yang et al., 1983). In addition to disturbances to the plant metabolism, a recent study has shown that at low concentrations, selenium acts as an anti-oxidant in plants inhibiting lipid peroxidation but at high concentrations (additions of > 10 mg kg^{-1}) it acts as a pro-oxidant encouraging the accumulation of lipid peroxidation products resulting in marked yield losses (Hartikainen et al., 2000).

Food crops tend to have relatively low tolerance to selenium toxicity and most crops have the potential to accumulate the element in quantities that are toxic to animals and humans. In general, root crops contain higher selenium concentrations than other plants (Table 11) and plant leaves often contain higher concentrations than the tuber. For example, Yang et al. (1983) noted that selenium concentrations in vegetables (0.3 – 81.4 mg kg^{-1}) were higher than in cereal crops (0.3 - 28.5 mg kg^{-1}in rice and maize) in seleniferous regions of China. Turnip greens were particularly high in selenium, with an average of 457 and range up to 24 891 mg kg^{-1} compared to an average of 12 mg kg^{-1} in the tuber. In moderate to low selenium environments, alfalfa (Sp. *Medicago*) has been shown to take up more selenium than other forage crops, which may be due to deeper rooting accessing more alkaline conditions hence more bioavailable selenium at depth. However, in general, crop species grown in very low-selenium soils show little difference in take up and changing the type of plants makes little impact on improving the selenium content of crops (Jacobs 1989), an exception is reported in New Zealand (Section V of this Chapter).

E. Selenium in Water.

It is estimated that the annual global flux of selenium from land to the oceans is 14 000 tonnes year^{-1} via surface and groundwaters, which represent a major pathway of selenium loss from land in the selenium cycle (Nriagu, 1989). Approximately 85% of the selenium in most rivers is thought to be in particulate rather than aqueous form, however, the cycling of selenium from the land to the aqueous environment is poorly understood and requires further investigation (Haygarth, 1994).

The average concentration of selenium in seawater is estimated at 0.000 09 mg L^{-1} (Cutter and Bruland, 1984) but the mean residence time for selenium is thought to be 70 years in the mixed layer and 1100 years in the deep ocean, hence the oceans constitute an important environmental sink for selenium (Haygarth, 1994). Biogenic volatilization from seawater to the atmosphere is estimated at 5000 – 8000 tonnes annually (Nriagu, 1989) and Amouroux et al., (2001) have demonstrated that the biotransformation of dissolved selenium in seawater during spring blooms of phytoplankton is a major pathway for the production of gaseous selenium emission to the atmosphere making the oceans an important component of the selenium cycle.

Although the oceans via seafood do play a role in human selenium exposure, water used for drinking is more important. Selenium forms a very minor component of most natural waters and rarely exceeds 10 µg L^{-1}. Typically ranges are < 0.1 – 100 µg

L^{-1} with most concentrations below 3 μg L^{-1}. A 'garlic odor' has been noted in waters containing 10 – 25 μg L^{-1} whereas waters containing 100 – 200 μg L^{-1} selenium have an acerbic taste (Jacobs, 1989; WHO, 1987). In general, groundwaters contain higher selenium concentrations than surface waters due to greater contact times for rock-water interactions (Hem, 1992). Groundwaters containing 1000 μg L^{-1} selenium have been noted in seleniferous aquifers of Montana, USA and up to 275 μg L^{-1} in China (Jacobs, 1989; Fordyce et al., 2002b) (Table 3). Although rare in nature, concentrations of up to 2000 μg L^{-1} selenium have also been reported in saline lake waters in the USA, Venezuela and Pakistan (Afzal et al., 2000). Anthropogenic sources of selenium can impact upon surface water quality as a result of atmospheric deposition from fossil fuel combustion, industrial processes and sewage disposal. For example concentrations of 400 μg L^{-1} in surface waters have been reported around the nickel-copper smelter at the Sudbury ore deposit in Ontario, Canada (Nriagu, 1989) and sewage effluents have been known to contain 45 – 50 μg L^{-1} selenium (Jacobs, 1989). Irrigation practices can also affect the amount of selenium in water such as at Kesterson Reservoir in the San Joaquin Valley of California, USA (Jacobs, 1989) (See section VI of this Chapter).

F. Atmospheric Selenium.

The volatilization of selenium from volcanoes, soil, sediments, the oceans, microorganisms, plants, animals and industrial activity all contribute to the selenium content of the atmosphere. It is estimated that natural background levels of selenium in non-volcanic areas are very low, around 0.01 – 1 ng m^{-3}, however, the residency time of selenium can be a matter of weeks making the atmosphere a rapid transport route for selenium in the environment. Volatilization of selenium from the surface of the planet to the atmosphere results from microbial methylation of selenium from soil, plant, and water surfaces and is affected by the availability of selenium, carbon source, oxygen availability and temperature (Haygarth, 1994).

The majority of gaseous selenium is thought to be in dimethylselenide form and it is estimated that terrestrial biogenic sources contribute 1200 tonnes of selenium per year to the atmosphere. Atmospheric dusts derived from volcanoes and wind erosion of the Earth's surface (180 tonnes per year) and suspended sea salts (550 tonnes per year) from the oceans also constitute significant sources of atmospheric selenium (Nriagu, 1989). It is suggested that particle-bound selenium can be transported several thousand kilometers before deposition back to the Earth's surface in both wet and dry forms. Wet deposition is thought to contribute 5610 tonnes per year to land (Haygarth, 1994). For example, in the UK it has been demonstrated that wet deposition (rain, snow, etc) accounts for 76 – 93% of total deposition with > 70% of selenium in soluble form. In the proximity of selenium sources (such as industrial emissions), atmospheric deposition can account for 33 – 82% of uptake in the leaves of plants (Haygarth, 1994).

G. Selenium is All Around Us.

From the descriptions above, it is clear that selenium is present in varying quantities in the environment all around us as a result of natural and man-made processes. Animals and humans are exposed to environmental selenium via dermal contact, the inhalation of the air we breathe and via ingestion of water and of food and animals in the diet grown on soils containing selenium.

III. Selenium in Animals and Humans

A. Selenium Exposure.

In most non-occupational circumstances atmospheric exposure is insignificant as concentrations of selenium are so low (< 10 ng m^{-3}). However, occupational inhalation exposure may occur in the metal, selenium-recovery and paint industries. In these circumstances, acute (short term) exposure of humans to hydrogen selenide, the most toxic selenium compound, which exists as a gas at room temperature, results in irritation of the mucous membranes, pulmonary edema, severe bronchitis and bronchial ammonia whereas inhalation of selenium-dust can cause irritation of the membranes in the nose and throat, bronchial spasms and chemical pneumonia. Selenium-dioxide gas is the main source of problems in industrial situations as selenious acid is formed on contact with water or sweat causing irritation. Indigestion and nausea, cardiovascular effects, headaches, dizziness, malaise and irritation of the eyes have also been reported in occupational selenium exposure (WHO, 1987 and WHO, 1996).

As a result of these effects, hydrogen selenide gas is classed as a highly toxic substance and the common selenium-bearing compounds sodium selenite and sodium selenate are considered ‘high concern’ pollutants (US-EPA, 2002a). Some regulatory values for selenium compounds in air are presented in Table 12. Little information on the long-term (chronic) effects of selenium inhalation is available. In seleniferous areas of China, there is some evidence to suggest that the selenium-loading of the population is enhanced by inhalation of coal smoke from open fires used for cooking as concentrations have been known to rise to 160 000 ng m^{-3} in air during combustion

(Yang et al., 1983). However, it is difficult to assess the amount of exposure via this route compared to other sources (Fordyce et al,1998). Smoking is an inadvertent inhalation exposure route to selenium as tobacco commonly contains 0.03 – 0.13 mg kg^{-1} (WHO, 1987). Assuming a cigarette contains 1 g tobacco and that all the selenium is inhaled, a person smoking 20 cigarettes could intake 1.6 µg Se day^{-1}. The inhalation of locally grown selenium-rich tobacco in seleniferous regions of China may contribute to the loading of the local population (selenium concentration 9.05 mg kg^{-1}, Fordyce et al., 1998). In general, however, inhalation is a less important exposure route than ingestion. For example, studies carried out on dogs found that only 52% and 73% of selenium in the form of metal and selenious acid aerosols were adsorbed in the lungs compared to 73 and 96% absorption in the gut (WHO, 1987, Levander, 1986).

Very few studies have examined the effects of dermal exposure to selenium although sodium selenite and selenium-oxychloride solutions have been proved to absorb into the skin of experimental animals. The insoluble compound selenium sulfide is used in anti-dandruff shampoos and is not normally absorbed through the skin but elevated selenium concentrations in urine have been noted in people using these products with open skin lesions. In an occupational setting, selenium-dioxide gas can result in burns and dermatitis and an allergic body rash. In most normal circumstances, however, dermal contact is not an important exposure route (WHO, 1987, WHO 1997, Levander, 1986).

In the majority of cases, water selenium concentrations are extremely low (< 10 µg L^{-1}) and do not constitute a major exposure pathway, however, aquatic life-forms are sensitive to selenium intoxication as soluble forms of selenate and selenite are highly bioavailable and cause reduced reproduction and growth in fish (Jacobs, 1989). For this reason, the US-EPA has set a chronic ecotoxicity threshold of 5 µg L^{-1}in surface water (Canton, 1999). Selenium is a bioaccumulator, which means that plants and animals retain the element in greater concentrations than are present in the environment (Table 13) and the element can be bioconcentrated by 200 – 6000 times. For example, concentrations in most waters are approximately 1 µg L^{-1} whereas freshwater invertebrates generally contain up to 4 mg kg^{-1} selenium (Jacobs, 1989). Phytoplanktons are efficient accumulators of dissolved selenomethionine and incorporate inorganic selenium into amino acids and proteins (estimated bioconcentration factors range from 100- 2600) (Jacobs, 1989). However, the reported lethal doses of selenium in water for invertebrates (0.34 – 42 mg L^{-1}) and fish (0.62 – 28.5 mg L^{-1}) indicate that in most circumstances, water alone is not a major environmental problem. It should be noted, however, that inorganic and organic selenium enter the food chain almost entirely via plants and algae and bioconcentration from high-selenium waters could cause problems because selenium passes up the food chain from algae and larval fish to large fish, birds and humans (Jacobs, 1989; WHO, 1987). A MAC of 10 – 11 mg kg^{-1} selenium in the diets of fish has been proposed in the USA to prevent toxicity and the uptake of too much selenium into the food chain (Jacobs, 1989). At concentrations > 50 µg L^{-1} in water, selenium intake can contribute significantly to overall dietary intake in animals and humans and the US-EPA currently recommend this as the MAC for selenium in drinking water (US-EPA, 2002b). The World Health Organization currently set a more precautionary MAC of 10 µg L^{-1} selenium for drinking water (WHO, 1996).

However, the most important exposure route to selenium for animals and humans is the food we eat, as concentrations are orders of magnitude greater than in water and air in most circumstances (WHO, 1996). In terms of the human diet, organ meats such as liver and kidney are good sources of selenium and some seafoods contain almost as much. Muscle meats are also a significant source and garlic and mushrooms contain more than most other vegetables. Cereals are another important source, however, white bread and flour contain less selenium than wholemeal by about 10 – 30% (Table 14). Brazil nuts sold in the UK are high in selenium, indeed cases of selenium poisoning in Amazon peoples following consumption of nuts of the *Lecythidaceae* family have been reported in Brazil. These incidents resulted in nausea vomiting, chills, diarrhea, hair and nail loss, painful joints and death in some cases (See Part F of this Section). Cooking reduces the selenium contents of most foods and studies have shown that vegetables that are normally high in selenium such as asparagus and mushrooms lose 40% during boiling. Other studies estimate 50% of the selenium content is lost from vegetables and dairy products during cooking especially if salt, and low pH foods such as vinegar are added whereas frying foods results in much smaller losses (WHO, 1987; WHO, 1996; Rayman, 2002; Levander, 1986).

Levels of dietary selenium intake show huge geographic variation and are dependent upon the geochemical conditions of the food source environments as well as differences in dietary composition. For example in 1995, cereals accounted for 75% of the total 149 $\mu g\ day^{-1}$ selenium intake in Canada but only 10% of the 30 $\mu g\ day^{-1}$ intake in Finland (WHO, 1996). In general terms, cereals grown in North America contain more selenium than European crops and concern is growing in Europe over declining selenium intakes. The UK traditionally imported large quantities of wheat from North America but since the advent of the European Union, most cereals are now more locally derived and as a consequence, daily intakes of selenium in the UK have been falling. Marked declines are evident even over a four-year period from intakes of 43-µg day^{-1} in 1991 to 29 – 39 µg day^{-1} in 1995 (Figure 6) (Rayman, 2002). This downward trend is also attributed to a reduction in cereal consumption in the UK, which fell from 1080 g person^{-1} week^{-1} in 1970 to 756 g person^{-1} week^{-1} in 1995 (MAFF, 1997). The selenium content of Irish bread is also significantly lower than in the USA and only marginally higher than UK (Table 14) (Murphy and Cashman, 2001). Other cereal crops such as rice generally contain low selenium contents (Table 14) and can have a significant influence on overall dietary intake when consumed as the staple food as in most of Asia. Conversely Japanese diets can be very high in selenium (up to 500 µg day^{-1}) in areas where a large amount of seafood is consumed (WHO, 1987).

Some examples of daily dietary selenium intakes from around the world are listed in Table 15. On a global scale it is estimated that dietary intakes in adults range from 3 – 7000 µg day^{-1} and for infants in the first month of life from 5 – 55 µg day^{-1} the wide ranges being attributed to selenium contents in the environment (WHO, 1996). The greatest variations in dietary intake are reported from selenium deficient and seleniferous regions of China (Tan, 1989) but contrasts also occur in South America between high daily intakes (100 – 1200 µg) associated with foodstuffs grown on selenium-rich shales in the Andes and Orinoco River of Venezuela and wide-spread selenium deficiency in Argentina (WHO, 1987; Oldfield 1999). Dietary intakes in countries such as New Zealand, Finland and Turkey are also poor as a consequence of low-selenium soils whereas intakes in Greece, Canada and the USA are generally adequate (WHO, 1987). On the basis of selenium requirement studies, a range of 50 – 200 μg day^{-1} has been recommended by the US-NRC (National Research Council) for adults depending on various factors such as physiological status. Balance studies to determine the ratio of selenium inputs and outputs in human beings more precisely were attempted, however, these were not successful as humans have the ability to modify fecal and urinary excretion of selenium depending on levels of intake (WHO, 1996). Current recommended daily allowances (RDAs) of dietary selenium range from 55 μg in women to 75 μg day^{-1} in men and 8.7 – 10 μg day^{-1} in infants (Table 15) (WHO, 1996; MAFF 1997).

Just as bioavailability is an important factor in terms of plant uptake of selenium, so too is it an important factor in the diets of animals and humans. Dietary studies have shown that selenomethionine is more readily absorbed in the guts of animals and humans than selenate, selenite or selenocysteine. More than 90% of ingested selenomethionine and selenate is absorbed whereas the rate for sodium selenite is slightly lower (> 80%). Selenides and elemental selenium are poorly absorbed. Very few studies have examined the chemical form of selenium in foodstuffs but evidence suggests that 7.6 – 44% of selenium in tuna is in the form of selenate with the remainder present as selenite and selenide. In contrast, 50% of the selenium in wheat and 15 % in cabbage is in the form of selenomethionine. These differences in the chemical forms of selenium are reflected in the rate of absorption and bioavailability of the element in foodstuffs. For example, it is estimated that over 90% of the selenium in Brazil nuts and beef kidney is bioavailable, compared to only 20 – 60% in tuna, however, other seafood, shrimp, crab, and Baltic herring have higher bioavailability. As an indication of the diet in general, studies carried out in New

Zealand have shown that 79% of selenium present in natural foods is bioavailable. In addition to foodstuffs, mineral supplements are a source of dietary selenium to humans and animals. Chemical supplement tests show 97% adsorption of selenomethionine, 94% of selenate and 60% of sodium selenite in this dietary form (WHO, 1987; WHO, 1996; Rayman, 2002; Levander, 1986).

In animals, 85 – 100 % of dietary plant selenium is adsorbed whereas only 20 – 50% of the selenium present in meat and fish is taken up by birds and mammals and in general terms, selenium in plant forms is more readily bioavailable than selenium in animal forms (WHO, 1987; WHO, 1996; Levander, 1986).

The bioavailability of selenium to humans and animals is not only dependent on the amount of absorption but also on the conversion of the ingested selenium to metabolically active forms. In humans, studies based on the activity of the selenium dependent enzyme GSH-Px have shown that the bioavailability of selenium in wheat is > 80% whereas the bioavailability of selenium in mushrooms is very low. In a comparison between wheat and mineral selenate supplements, whilst the latter were shown to enhance GSH-Px activity, patients fed wheat demonstrated greater increases and better long-term retention of selenium (WHO, 1987).

Much has still to be learned about the uptake of selenium in humans and animals, however, it is clear that in most normal circumstances food forms the major exposure route as selenium accumulates from the environment via plants and algae through the food chain to animals and man. Selenium in the form of selenomethionine and selenate is highly bioavailable to animals and humans and foodstuffs that contain high proportions of these forms such as organ and muscle meats, Brazil nuts and wheat are good sources of the element in the diet (WHO, 1987, Rayman, 2002).

B. Selenium In the Body of Animals and Humans.

Once ingested into the body, most selenium is absorbed in the small intestine of animals and humans but the rates and mechanisms of selenium metabolism vary between different animal species. In general, single-stomached animals absorb more selenium than ruminants due to the reduction of selenite to insoluble forms by rumen microorganisms. Experiments on rats indicate very little difference in the process of absorption of different selenium forms, 92% of selenite, 91% of selenomethionine and 81% of selenocysteine were absorbed primarily in the small intestine and none in the stomach. Approximately 95% of the total selenium intake was absorbed regardless of whether the rats were fed a low selenium or high selenium diet indicating that selenium intake is not under homeostatic control*, this is true in general for intake in animals and humans. However, other studies have shown that oral doses of selenomethionine are retained more readily and turned over more slowly than selenite in humans therefore unlike rats there is a difference in the metabolism of different forms of selenium. In fact, selenomethionine, the main form of uptake from plants to animals becomes associated with protein tissues in the body whereas inorganic selenium is absorbed into other tissues (Levander, 1986, WHO, 1987, WHO, 1996). Most of the ingested selenium is quickly excreted in the urine, breath, perspiration and bile, and the remainder becomes bound or incorporated into blood and proteins. Urine is the primary route of excretion (70 –80%) in single-stomached animals, however, in ruminants selenium is mostly excreted in the faeces and studies have shown that the majority of this selenium is in unavailable elemental form. Chemical selenium-tracer experiments in humans suggest that the main extraction pathway is via urine, however, in studies using natural foods, excretion in faeces was equal to that of urine whereas minimal amounts of selenium were exuded in sweat and respiration and expulsion of volatile forms of selenium only occurred at very high exposures. Unlike selenium absorption, which is not homeostatically regulated, selenium excretion in animals and humans is directly influenced by nutritional status, excretion rises as intake increases and decreases when selenium intakes are low (Levander, 1986; WHO, 1987; WHO, 1996).

The remaining selenium is transported rapidly round the body and concentrations in the internal organs, which are rich in protein. This pattern is present in a number of animal species (Figure 7). Hence, in normal conditions in humans, selenium levels are highest in the liver and kidneys and lower in muscle tissues but the largest total amount of selenium in the human body is in the muscles as these form the main body mass. Total human body selenium contents are estimated at 3 – 14.6 mg (WHO, 1987).

In rats fed selenium deficient diets, however, the pattern of selenium distribution is different with selenium reserved in the testes, brain, thymus and spleen. Indeed in humans also, the supply to the testes has priority over the other tissues during selenium deficiency because the element is found in the mitochondrial capsule protein (MCP) and is involved in biosynthesis of testosterone. Consequently, the selenium content of the testes increases considerably during puberty (WHO, 1987; Levander 1986).

Both inorganic and organic selenium are converted by animals and humans to mono-, di- or tri-methylated forms by the main metabolic pathway, reduction and trimethylselenonium, is the main urinary excretion form. However, in cases of selenium toxicity, this pathway becomes overloaded and the volatile selenium metabolite dimethylselenide is produced and exhaled via the lungs resulting in the characteristic 'garlic breath' symptom in animals and humans suffering selenosis. There is much debate over the form of selenium held in protein tissues, non-ruminant animals and humans cannot synthesize selenite into selenomethionine but there is evidence to suggest that selenomethionine can be incorporated into protein tissues directly. However, in the case of rats it is then converted to selenite or selenate. Rabbits and rats can also convert selenite into selenocysteine tissue proteins. Selenium may also be present in proteins in the selenotrisulfide and acid- labile form. Early work suggested that selenium intake in naturally occurring organic forms was retained in tissues to a greater extent than inorganic forms, however, experiments with mice using selenite, Se-methylselenocysteine and selenomethionine showed that mice fed selenomethionine had greater quantities and better long term retention of selenium than those fed selenite or Se-methylselenocysteine. Therefore, the distinction between inorganic and organic forms of selenium does not hold true as the metabolism of Se-methylselenocysteine and selenocysteine resemble that of selenite rather than selenomethionine. There is some evidence for metabolic pools of selenium in animals and humans, studies with ewes fed selenium adequate and then selenium deficient diets showed that they were able to pass on adequate levels of selenium to their lambs even though the lambs were born 10 months into the selenium deficient diet. Possible mechanisms for these pools may be the sequestration of selenomethionine or selenamino acids incorporated into protein structures and then released during protein turnover (WHO, 1987; Levander, 1986; WHO, 1996).

In most circumstances there is a close correlation between the levels of selenium in the diet of humans and animals and blood selenium content. On average, plasma levels vary from 0.079 – 0.252 mg L^{-1} depending on selenium intake whereas the mean concentration of selenium in human whole blood is 0.2 mg L^{-1} (WHO, 1987; WHO, 1996). Human whole blood selenium levels show marked geographic variation depending on dietary intake. Ranges of 0.021 – 3.2 mg L^{-1} have been reported worldwide with highest concentrations in seleniferous areas of China and Venezuela and lowest concentrations in selenium deficient regions of Scandinavia, New Zealand and China (Table 16) (WHO, 1996; Oldfield, 1999). Similarly, concentrations in hair, nails and urine vary according to differences in dietary intake, some examples of the selenium composition of these tissues are given in Table 16. Selenium levels in human milk are affected by maternal intake and infants and young children have a high requirement for the element during the rapid growth periods of early life. However, the age of mother and the concentration of selenium during pregnancy do not affect the weight of baby or the length of pregnancy. Wide ranges of 2.6 –283 mg L^{-1} in human milk have been reported from selenium deficient and seleniferous regions in China, compared to ranges of 7 – 33 mg L^{-1} in the USA (Levander, 1986.)

In terms of biological function, approximately 20 essential selenoproteins containing selenocysteine have now been identified in microbes, animals and humans, many of which are involved in redox reactions acting as components of the catalytic cycle (WHO, 1996). The 14 or so selenoproteins found in mammals are listed in Table 17

(Rayman 2002). Enzyme activity is attributed to the glutathione peroxidase, thioredoxin reductase, iodothyronine deiodinase* and selenophosphate synthetase groups. In complex interactions with vitamin E and polyunsaturated fatty acids, selenium plays an essential biological role as part of the enzyme GSH-Px, which protects tissues against peroxidative damage by catalyzing the reduction of lipid hydrogen peroxide or organic hydroperoxides. Together, GSH-Px, vitamin E and superoxide dismuthases form one of the main antioxidant defense systems in humans and animals. As such, selenium has been linked to enzyme activation, immune system function, pancreatic function, DNA repair and the detoxification of xenobiotic agents such as parquat, however, the exact mechanisms of immune function and detoxification are unknown (Combs and Combs, 1986; Levander, 1986; WHO, 1987; WHO, 1996). Selenium is found in the prosthetic groups of several metalloenzymes and appears to protect animals against the toxic effects of arsenic, cadmium, copper, mercury, tellurium and thallium in most circumstances but this is not always the case and the biological response depends on the ratio of selenium/metal involved (WHO, 1987; Fergusson, 1990). Selenium behaves antagonistically with copper and sulfur in humans and animals inhibiting the uptake and function of these elements. Selenium has been identified as a component the cytochrome P_{450}* system in humans and animals, however, the exact biological role of this seleno-protein has yet to be established (WHO, 1996; WHO, 1987). Important developments in recent years have shown that selenium is beneficial to the thyroid hormone metabolism. There are three iodothyronine deiodinase (IDI) selenoenzymes. Types 1 and 2 are involved in the synthesis of active 3, 3’ and 5 – triiodothyronine (T3) hormones*, whereas Type 3 IDI catalyses the conversion of thyroxine (T4)* to inactive T3(rT3). These hormones exert a major influence on cellular differentiation, growth and development, especially in the fetus and child (Arthur and Beckett, 1994). Selenium also appears to be important in reproduction, in addition to aiding the biosynthesis of testosterone (see above) the selenium contents of avian eggs are high whereas morphological deformities and immotility and reduced fertility have been reported in sperm in selenium deficient experimental animals (WHO, 1987; Rayman, 2002; WHO 1996). Although many of the *in vivo* functions of selenium are still poorly understood, deficient and excessive dietary intakes of selenium have a marked effect on animal and human health, some of which are discussed below.

C. Selenium Deficiency – Effects in Animals.

Due to the complementary role of selenium and Vitamin E, all selenium deficiency diseases in animals are concordant with vitamin E deficiency with the exception of neutrophil microbicidal activity reduction and the 5-deiodinase enzymes responsible for the production of triiodothyronine from thyroxine. Selenium is necessary for growth and fertility in animals and clinical signs of deficiency include dietary hepatic apoptosis* in rats and pigs; exudative diathesis*, embryonic mortality and pancreatic fibrosis in birds; nutritional muscular dystrophy, known as white muscle disease and retained placenta in ruminants and other species and mulberry heart disease in pigs. Clinical signs of selenium deficiency in animals include reduced appetite, growth, production and reproductive fertility, unthriftyness and muscle weakness (Levander, 1986; WHO, 1987; WHO, 1996; Oldfield, 1999).

White muscle disease is a complex condition, which is multi-factorial in origin and causes degeneration and apoptosis of the muscles in a host of animal species. The disease rarely affects adult animals but can affect young animals from birth. In lambs born with the disease, death can result after a few days. If the disease manifests slightly later in life, animals have a stiff and stilted gait, arched back are not inclined to move about, lose condition, become prostrate and die. The disease responds to a combination of vitamin E and selenium supplementation (WHO, 1987; Levander, 1986; WHO, 1996; Oldfield, 1999).

Exudative Diathesis in birds leads to massive hemorrhages beneath the skin as a result of abnormal permeability of the capillary walls and accumulation of fluid throughout the body. Chicks are most commonly affected between 3 – 6 weeks of age and become dejected, lose condition, show leg weakness and may become prostrate and die. The disease responds to either vitamin E or selenium supplementation but will not respond to vitamin E alone if selenium is deficient (WHO, 1987).

Hepatic apoptosis in pigs generally occurs at 3 – 15 weeks of age and is characterized by necrotic liver lesions and death and can be protected against by supplements of alpha-tocopherol and selenium (Levander, 1986).

Low-selenium pastures containing 0.008 – 0.030 mg kg^{-1} are associated with a condition called ‘ill thrift’ in lambs and cattle from New Zealand. The disease is characterized by subclinical growth deficits, clinical unthriftyness, rapid weight loss and sometimes death but can be prevented by selenium supplementation giving marked increases in growth and wool yields (Levander, 1986; WHO, 1987).

The level of dietary selenium needed to prevent deficiency depends on the vitamin E status and species of the host. For example, chicks receiving 100 mg vitamin E require 0.01 mg kg^{-1} selenium to protect against deficiency whereas vitamin E deficient chicks require 0.05 mg kg^{-1} selenium. Under normal vitamin E status, concentrations of 0.04 – 0.1 mg kg^{-1} (dry weight) in feedstuffs are generally adequate for most animals with a range of 0.15 - 0. 20 mg kg^{-1} for poultry and 0.03 – 0.05 mg kg^{-1} for ruminants and pigs (WHO, 1987; Levander 1986).

Selenium deficiency and white muscle disease are known to occur in sheep when blood selenium levels fall below 50 µg L^{-1} and kidney concentrations below 0.21 mg kg^{-1} (dry weight). Blood levels of 100 µg L^{-1} selenium are needed in sheep and cattle and 180 – 230 µg L^{-1} in pigs to maintain the immuno-response systems. Studies have shown that most farmland grazing in the UK is not able to provide enough selenium to support 0.075 mg L^{-1} blood in cattle, indeed selenium deficiency in animals is very common and widespread around the globe affecting much of South America, North America, Africa, Europe, Asia, Australia and New Zealand. Many western countries now adopt selenium supplementation programs in agriculture but these are often not available in South America, Africa and Asia and livestock productivity is significantly impaired by selenium deficiency in these regions (WHO, 1987; Levander, 1986, WHO, 1996; Oldfield, 1999).

D. Selenium Deficiency – Effects in Humans.

No clear-cut pathological condition resulting from selenium deficiency alone has been identified in humans, however, the element has been implicated in a number of diseases (WHO, 1996).

1. Keshan Disease (KD)

KD is an endemic cardiomyopathy (heart disease) that mainly affects children and women of childbearing age in China. The disease has been documented for over 100 years but the name is derived from a serious outbreak in Keshan County, northeast China in 1935. Outbreaks have been reported in a broad belt stretching from Heilongjiang Province in the northeast of China to Yunnan province in the southwest that transcends, topography, soil types, climatic zones and population types (Figure 8). The disease manifests as an acute insufficiency of the heart function or as a chronic moderate to severe heart enlargement and can result in death. Seasonal variations in outbreak were noted with peaks in the winter in the south and the summer in the north. The worst affected years on record were 1959, 1964 and 1970 when the annual prevalence exceeded 40 per 100 000 with more than 8000 cases and 1400 – 3000 deaths each year (Tan, 1989).

Although the disease occurs in a broad belt across China, all of the affected areas were characterized by remoteness and a high proportion of subsistence farmers who were very dependent on their local environment for their food supply. Investigators noticed that white muscle disease in animals occurred in the same areas and further studies demonstrated that the soils and crops were very low in selenium. KD occurred in areas where grain crops contained < 0.04 mg kg^{-1} selenium, dietary selenium intakes were extremely low, between 10 – 15 µg day^{-1} and affected populations were characterized by very low selenium status indicated by hair contents of < 0.12 mg kg^{-1} (Xu and Jiang, 1986; Tan, 1989; Yang and Xia, 1995). On the basis of these findings, large-scale mineral supplementation was carried out on 1 – 9 year old children who were at high risk of the disease. In a trial carried out in Mianning County, Sichuan province, from 1974 to 1977, 36603 children were given 0.5 – 1.0 mg sodium selenite tablets per week whereas 9642 children were given placebo tablets. During the four years of investigation, 21 cases of the disease and three deaths occurred in the selenium-supplemented group where as 107 cases and 53 deaths occurred in the control group. By 1977 all the children were supplemented with selenium and the disease was no longer prevalent in either group. The results showed that supplements of 50-µg day^{-1} selenite could prevent the disease but if the disease was already manifest, selenium was of no therapeutic value (Anon, 2001).

Although the disease proved to be selenium-responsive, the exact biological function of the element in the pathogenesis was less clear and the seasonal variation in disease prevalence suggested a viral connection. Subsequent studies have demonstrated a high prevalence of the coxsackie B virus in KD patients (see for example Li et al, 2000) and studies have proved increased cardiotoxicity of this virus in mice suffering from selenium and vitamin E deficiency. For a number of years it was thought that selenium deficiency impaired the immune function lowering viral resistance, however, more recent work by Beck (1999), has shown that a normally-benign strain of coxsackie B3 (CVB3/0) alters and becomes virulent in either selenium-deficient or vitamin E-deficient mice and once the mutations are completed, even mice with normal nutritional status become susceptible to KD. These changes in the virus are thought to occur as a result of oxidative stress due to low vitamin E and selenium status. This work demonstrates not only the importance of selenium deficiency in immuno-suppression of the host but in the toxicity of the viral pathogen as well. Other studies have implicated moniliformin mycotoxins produced by the fungi fusarium proliferatum and fusarium subglutinans in corn as a possible cause of KD (Pineda-Valdes and Bullerman, 2000). As with many environmental conditions, KD is likely to be multi-factorial but even if selenium deficiency is not the main cause of the disease, it is clearly an important factor.

During the 1980s the prevalence dropped to less than 5 per 100 000 with less than 1000 cases reported annually. The reason for this is two-fold, firstly widespread selenium supplementation programs have been carried out on the affected populations and secondly economic and communication improvements in China as with the rest of the world, mean that the population is increasingly less dependent on locally grown foodstuffs in the diet. In recent years the incidence of the disease has dropped still further such that it is no longer considered a public health problem in China (Burk, 1994).

2. Kashin-Beck Disease (KBD)

KBD, an endemic osteoarthropathy (stunting of feet and hands) causing deformity of the affected joints, occurs in Siberia, China, North Korea and possibly parts of Africa. The disease is named after the Russian scientists who first described it between 1861 and 1899. It is characterized by chronic disabling degenerative osteoarthrosis affecting the peripheral joints and the spine with apoptosis of the hyaline cartilage tissues. Impairment of movement in the extremities is commonly followed by bone development disturbances such as shortened fingers and toes and in more extreme cases, dwarfism (Figure 9) (Levander, 1986; Tan, 1989; WHO, 1996). Indeed the main feature of KBD is short stature caused by multiple focal apoptosis in the growth plate of the tubular bones. In China, the pattern of disease incidence is concordant with KD in the north of the country but the links with selenium deficient environments are less clear (Tan, 1989).

Initial studies revealed that rats fed grain and drinking water from the affected areas in China suffered acute massive liver apoptosis and foodstuffs from the affected areas were found to be low in selenium. Children and nursing mothers were supplemented with 0.5 – 2.0 mg sodium selenite per week for a period of 6 years and the disease prevalence dropped from 42% to 4% in children aged 3 – 10 years as a result (Tan, 1989). More recent studies carried out since the early 1990s demonstrated KBD-like cartilage changes and bone mineral density reduction in selenium-deficient rats (Sasaki et al., 1994; Moreno-Reyes et al., 2001). However, other factors have been implicated in the pathogenesis of KBD. The main theory proposed by Russian investigators was that the disease was a result of mycotoxins in the diet and other work carried out in China has suggested ingestion of contaminated drinking water as a possible cause. In China, higher fungal contamination of grain in KBD areas has been known for a number of years and other work suggests that the presence of humic substances in drinking water is a factor, the mechanism of action being free radical generation from the oxy and hydroxyl groups of fulvic acid. Nonetheless, selenium was confirmed as a preventative factor in KBD in these studies Peng et al. (1999).

There are similarities between KBD and the iodine deficiency disorder cretinism. Several studies have considered the relationships between KBD, selenium and iodine deficiency. Work in the Yulin District of China (Zhang et al., 2001) carried out on 353 rural school children aged 5 –14 years compared data between three endemic KBD villages (prevalence rates 30 – 45%) and a non-endemic village. Higher fungal contamination was recorded in cereal grain stores in KBD areas than in the non-endemic village and hair selenium and urinary iodine concentrations were lower in families suffering the disease than in control groups. However, iodine deficiency did not correlate significantly with increased KBD risk. Recent work into the disease has focused on Tibet and does implicate iodine in the pathogenesis. Among 575 5-15 year old children examined in 12 villages, 49% had KBD, 46% had the IDD goiter and 1% had cretinism. Of the examined population, 66% had urinary iodine contents of < 0.02 μg L^{-1} and the content was lower in KBD patients (0.12 μg L^{-1}) than in control subjects (0.18 μg L^{-1}). Hypothyroidism was more frequent in the KBD group (23%) compared to 4% in the controls. Severe selenium deficiency was present in all groups with 38% of subjects with serum concentrations of < 5 mg L^{-1} (normal range 60 – 105 mg L^{-1}). Statistical analyses revealed an increased risk of KBD in groups with low urinary iodine in the severe selenium deficient areas. Here also, mesophilic fungal contamination in barley (*Alternaria* sp.) was higher in KBD areas than non-endemic areas and disease prevalence correlated positively with the humic content of drinking water. The results suggest that KBD is multi factorial and occurs as a consequence of oxidative damage to cartilage and bone cells when associated with decreased antioxidant defense. Another mechanism that may coexist is bone remodeling stimulated by thyroid hormones whose actions are blocked by certain mycotoxins (Suetens et al., 2001).

3. Iodine Deficiency Disorders (IDD)

In addition to the links between selenium and iodine deficiency in KBD, the recent establishment of the role of the selenoenzymes, iodothyronine deiodinase (IDI) in thyroid function means that selenium deficiency is now being examined in relation to the IDD goiter and cretinism. Many areas around the world where IDD are prevalent are deficient in selenium including China, Sri Lanka, India, Africa and South America (WHO, 1996; WHO; 1987). Concordant selenium and iodine deficiency are thought to account for the high incidence of cretinism in Central Africa, in Zaire and Burundi in particular (Kohrle, 1999) and selenium deficiency has been demonstrated in populations suffering IDD in Sri Lanka (Fordyce et al, 2000a). However, these links require further investigation to determine the role of selenium in these diseases.

4. Cancer

Following studies that revealed an inverse relationship between selenium in crops and human blood versus cancer incidence in USA and Canada (Shamberger and Frost 1969), the potential anti-carcinogenic effect of selenium has generated a great deal of interest in medical science. Many studies to examine the links between selenium and cancer in animal experiments and humans have been carried out, however, to date, the results are equivocal. There is some evidence to suggest that selenium is protective against cancer due to its anti-oxidant properties, the ability to counteract heavy metal toxicity, to induce cell death to inhibit cell growth and to inhibit nucleic acids and protein synthesis (WHO, 1996; WHO, 1987; Clark et al., 1996; Varo et al., 1998). However other studies have shown that selenium may promote cancer based on the pro-oxidant mutagenic and immunosuppressive actions of some selenium compounds. For example, the supplementation of sodium selenate, sodium selenite and organic-selenium have been shown to reduce the incidence of several tumor types in laboratory animals but selenium-sulfide has been shown to be carcinogenic in animals and has been classified as a Group B2 compound - possible human carcinogen (WHO, 1987; WHO, 1996; US-EPA, 2002a). Human studies have demonstrated low levels of selenium in the blood of patients suffering gastrointestinal cancer, prostrate cancer or non-Hodgkinson's lymphoma but there is some evidence to suggest that selenium increases the risks of pancreatic and skin cancer (WHO, 1987; WHO, 1996; Birt, 1989).

An excellent review of the work into selenium and cancer is presented by Vinceti et al, (2000) and is summarized as follows. In a recent study of patients with a history of basal or squamous cell skin cancer, selenium intakes of 200 µg day^{-1} appeared to reduce mortality from all cancers and the incidence of lung, colorectal, and prostate cancers. However, it did not prevent the appearance of skin cancer. Indeed, some studies have shown an inverse relationship with melanoma risk but other studies have shown no relationship with non-melanoma skin cancer. However, Vinceti et al., (1998) carrying out assessments of populations inadvertently exposed to high selenium in drinking water report higher mortality from lung cancer, melanoma and urinary cancer among men and lymphoid neoplasm in women in the exposed group compared to controls. Other studies have shown an increased risk of colon and prostate cancer in populations taking selenium supplements in Iowa, USA and Finland than in control populations. However, a study in Montreal carried out between 1989 and1993 found no association between selenium status (measured by toenail selenium) and breast or prostate cancer but an inverse relationship with colon cancer (Vinceti et al., 2000).

In a study of stomach cancer in Finland and the Netherlands, an inverse relationship between selenium status and disease prevalence was found in Finnish men but not in women or in men or women from the Netherlands. No relationship between selenium status and stomach cancer was evident in studies carried out in Japan. A link between low selenium status and pancreatic cancer was observed in Maryland USA and Finland but a similar relationship with bladder and oral-pharyngeal cancer was evident in Maryland only, not Finland (Vinceti et al., 2000). Indeed Finland provides an interesting case because the government was so concerned about the low level of selenium intake in the Finnish diet that in 1984 a national program was initiated to increase the selenium content of Finnish foodstuffs by adding sodium selenate fertilizers to crops. Mean daily intakes rose from 45 μg day^{-1} in 1980 to 110 – 120 μg day^{-1} between 1987-1990 and 90 μg day^{-1} in 1992 (Varo et al., 1998) . Studies of cancer incidence over this time carried out in Finland, Sweden and Norway showed no reduction in colon cancer, non-Hodgkinson's lymphoma or melanoma in Finland whereas breast and prostrate cancer rates increased compared to the other two countries. Populations in Finland and New Zealand are known to have much lower selenium status than many other countries and yet no excess incidence of breast and colon is evident. Similarly no relationship between cancer prevalence and selenium intakes as low as 14 μg day^{-1}was identified among rural farmers in China. Conversely, recent work by Finley et al (2001) has demonstrated a link between consumption of high-selenium broccoli and reduced colon and mammary cancer prevalence. Based on the evidence presented above, it is fair to say that 'the jury is still out' in terms of the beneficial effects or otherwise of selenium and cancer!

5. Cardiovascular Disease

Selenium deficiency has also been implicated in cardiovascular health and it is suggested that serum concentrations of less than 45 μg L^{-1} increase the risk of ischemic heart disease. Animal studies have demonstrated that selenium could play a protective role by influencing platelet aggregation and increasing production of thromboxane A2 whilst reducing prostacyclin activity, however, the epidemiological evidence and studies into selenium status and disease risk provide contradictory results (Levander, 1986; WHO, 1987; WHO 1996).

6. Reproduction

The full role of selenium in reproduction has yet to be established, however, selenium deficiency has been shown to cause immotile and deformed sperm in rats (Wu et al., 1979; Hawkes and Turek, 2001) and studies into this field are on going in the medical profession at the current time.

7. Other Diseases

Selenium deficiency has been linked to a number of other conditions in man as the concentration of the element is decreased in the serum/plasma or erythrocytes of patients of AIDS, trisomy -21, Crohn's and Down's syndrome and phenylketonuria. The evidence of viral mutogeny under selenium deficiency established by Beck (1999) in the case of the coxsackie B virus has major implications in terms of the toxicity and immuno-response to many viral infections, particularly AIDS in light of the widespread selenium deficient environments of Central and Southern Africa where the disease has reached epidemic proportions in recent years (Longombe et al., 1994). The links between selenium status and AIDS require further investigation in that region.

Selenium deficiency has also been linked to muscular dystrophy (a similar human disease to WMD in animals) and muscular sclerosis but again the medical evidence for the role of the element is equivocal. Selenium supplementation has proved beneficial to patients suffering renal disease and finally an inverse relationship between selenium status and asthma incidence has also been postulated (WHO, 1987).

Dietary intakes of 0.1 - 0.2 mg kg^{-1} selenium are considered nutritionally generous converting to 50 – 100 µg day^{-1} for typical person and 0.7 – 2.8 µg kg-body weight^{-1}. Even in New Zealand and Finland, where selenium intake is 30-to 50-µg day^{-1}, compared with 100-to 250-µg day^{-1} in the USA and Canada, overt clinical signs of selenium deficiency are rare among humans (WHO, 1987, WHO, 1997). Nonetheless, research is increasingly showing the essential nature of selenium to human health and the potential for sub-clinical effects should not be underestimated and concern is growing in many regions of the world over low levels of dietary selenium intake in human populations.

E. Selenium Toxicity – Effects in Animals.

Experiments on laboratory animals have demonstrated that hydrogen selenide is the most toxic selenium compound by inhalation, sodium selenite the most toxic via ingestion and elemental selenium in the diet has low toxicity as it is largely insoluble (US-EPA 2002a; WHO, 1987). Sodium selenite or seleniferous wheat containing 6.4 mg kg^{-1} selenium causes growth inhibition and hair loss in animals and at concentrations of 8 mg kg^{-1}, pancreatic enlargement, anemia, elevated serum bilirubin levels and death follow (Levander, 1986; WHO, 1987). In addition to food intake, the application of sodium selenate in drinking water has been shown to cause fetal deaths and reduced fertility in mice. Selenium-sulfide is the only compound proven to be carcinogenic in animal studies resulting in increased liver tumors in rates. Although it is used in anti-dandruff shampoos it is not normally found in food and water. The oral lethal dose for sodium selenite in laboratory animals has been shown to range from 2.3 – 13 mg kg^{-1} body weight. Methylation of selenium is used as a detoxification mechanism by animals, inorganic and organic forms of selenium are metabolized to form mono-or di-or tri-methylated selenium, of which, mono-methylated forms are most toxic. For example, dimethylselenide is 500 – 1000 times less toxic than selenide (Se^{2-}) (WHO, 1987).

In natural conditions, acute selenium intoxication is uncommon as animals are not normally exposed to high selenium forage and tend to avoid eating selenium accumulator plants. Abnormal posture and movement, diarrhea, labored respiration, abdominal pains, prostration and death, often as a result of respiratory failure, characterize toxicity. The characteristic symptoms of selenium poisoning are the ‘garlic’ odor due to exhalation of dimethylselenide, vomiting, shortness of breath and tetanic spasms. Pathological changes include congestion of the liver and kidneys, swelling and hemorrhages of the heart (Levander, 1986; WHO, 1987; WHO, 1996).

Chronic selenium intoxication is more common and leads to two conditions known as alkali disease and blind staggers* in grazing animals. Alkali disease occurs after ingestion of plants containing 5 – 40 mg kg^{-1} over weeks or months and is characterized by dullness, lack of vitality, emaciation, rough coat, sloughing of the hooves, erosion of the joints and bones, anemia, lameness, liver cirrhosis and reduced reproductive performance. Although much of the work on alkali disease has focused on cattle, consumption of feeds containing 2 mg kg^{-1} selenium has also been shown to cause hoof deformation, hair loss, hypochromic anemia, and increased alkali and acid phosphatase activities in sheep (Levander, 1986; WHO 1987).

Blind staggers occurs in cattle and sheep but not in horses and dogs and occurs in 3 stages:

- Stage 1 - the animal wanders in circles, has impaired vision and is anorexic
- Stage 2 - the Stage 1 effects get worse and front legs weaken
- Stage 3 – the tongue becomes partially paralyzed and the animal cannot swallow and suffers blindness, labored respiration, abdominal pain, emaciation and death.

Pathological changes include liver apoptosis, cirrhosis, kidney inflammation and impaction of the digestive tract. Treatment of the condition involves drenching with large amounts of water and ingestion of strychnine sulfate. However, selenium may not be the main cause of blind staggers, which has similarities to thiamine deficiency. High, sulfate intake has been implicated in the disease and may enhance the destruction of thiamine (WHO, 1987).

In addition to alkali disease and blind staggers, high selenium intakes in pigs, sheep and cattle have been shown to interfere with normal fetal development and selenosis has been known to cause congenital malformation in sheep and horses and reproductive problems in rats, mice, dogs, pigs, and cattle whereby females with high selenium intakes had fewer smaller young which were often infertile. Blood selenium levels of > 2 mg L^{-1} in cattle and > 0.6 – 0.7 mg L^{-1} in sheep are associated with selenosis with borderline toxicity at 1 – 2 mg L^{-1} in cattle (WHO, 1987; Levander, 1986).

Although much of the work into selenium toxicity has focused on agricultural species, selenosis has also been reported in wild aquatic species and birds. Selenium concentrations of 47 – 53 μg L^{-1} in surface waters results in anemia and reduced hatchability of trout whereas concentrations of 70 – 760 μg L^{-1} in water are toxic to most aquatic invertebrates. Cranial and vertebral deformities occur in frogs exposed to 2000 μg L^{-1} in surface waters. Selenium toxicity is also associated with embryonic deformities in birds, indeed the hatchability of fertile eggs is a sensitive indicator of selenium intoxication. At concentrations of 6 – 9 mg kg^{-1} in the diet, embryos suffer brain tissue, spinal cord and limb bud deformities whereas > 7 mg kg^{-1} causes reduced egg production and growth (WHO, 1987; Jacobs, 1989).

F. Selenium Toxicity – Effects in Humans.

The toxicity of selenium compounds to humans depends on the chemical form, concentration and on a number of compounding factors. The ingestion of selenious acid is fatal to humans, preceded by stupor, hypertension and respiratory depression whereas the toxicity of methylated selenium compounds depends not only on the dose administered but also on the previous level of selenium intake. Higher selenium intake prior to dosing with methylated compounds has been shown to be protective against toxicity in animal experiments. Poor vitamin E status increases the toxicity of selenium and the nutritional need for the element whereas sulfate counteracts the toxicity of selenate but not of selenite or organic-selenium and increases selenium urinary excretion. Methyl-mercury enhances selenium deficiency but inorganic mercury increases methylated-selenium toxicity. At intakes of 4 – 8 mg kg^{-1}, selenium increases the copper contents of the heart, liver and kidneys but has a detoxifying or protective effect against cadmium and mercury (WHO, 1987; Bedwal et al., 1993). High selenium intake has also been shown to decrease sperm motility in health men (Hawkes and Turek 2001) and has been related to increased incidence of some forms of cancer including pancreatic and skin cancer (see Part D of this Section).

Overt selenium toxicity in humans is far less widespread than selenium deficiency. Following the discovery of seleniferous environments and the incidence of alkali disease in animals in the Great Plains of the USA during the 1950s, concern about potential adverse affects on the human population were raised. The health status of rural populations in seleniferous areas was examined. Results showed elevated urinary selenium levels in the population but no definite links to clinical symptoms of selenosis. However, a higher incidence of gastrointestinal problems, poor dental health, diseased nails and skin discoloration, were reported (Smith and Westfall, 1937). In similar studies in a seleniferous region of Venezuela, the prevalence of dermatitis, hair loss and deformed nails among children was higher than in non-seleniferous areas. The hemoglobin and hematocrit values in children from the seleniferous area were lower than in controls but did not correlate with blood or urine selenium levels and evidence of selenium toxicity effects was rather inconclusive. Nine cases of acute selenium intoxication due to the intake of nuts of the *Lecythis ollaria* tree in a seleniferous area of Venezuela have been reported resulting in vomiting and diarrhea followed by hair and nail loss and the death of one two-year old boy (WHO, 1987).

In China, an outbreak of endemic human selenosis was reported in Enshi District, Hubei Province and in Ziyang County, Shanxi Province during the 1960s, the condition was associated with consumption of high selenium crops grown on soils derived from coal containing> 300 mg kg^{-1} selenium. In the peak prevalence years (1961-1964) morbidity rates reached 50% in the worst affected villages, which were all located in remote areas among populations of subsistence farmers. Hair and nail loss were the prime symptoms of the disease but disorders of the nervous system, skin, poor dental heath, garlic breath and paralysis were also reported. Although no health investigations were carried out at the time, subsequent studies in these areas carried out in the 1970s revealed very high dietary intakes of 3.2 – 6.8 mg with a range of selenium in blood of 1.3 – 7.5 mg L^{-1} and hair selenium of 4.1 – 100 mg kg^{-1} (Yang et al., 1983; Tan, 1989).

Selenium toxicity related to mineral supplement intake has also been reported in the USA. In 1984, 12 cases of selenosis due to intakes over 77 days of tablets labeled to contain 0.15 – 0.17 mg selenium, but which actually were found to contain 27 – 31 mg selenium were reported. Patients suffered nausea, vomiting, nail damage, hair loss, fatigue, irritability, abdominal cramps, watery diarrhea, skin irritation and garlic breath and had blood serum levels of 0.528 mg L^{-1} (WHO, 1987). The US-EPA recommend an upper limit of mineral supplementation of selenium of 0.1 mg kg^{-1}.

Indeed, a whole list of symptoms have been implicated in elevated selenium exposure including severe irritations of respiratory system, metallic taste in mouth, tingling and inflammation of the nose, fluid on the lungs, pneumonia, the typical garlic odor of breath and sweat due to dimethylselenide excretion, discoloration of the skin, dermatitis, pathological deformation and loss of nails (Figure 10), loss of hair (Figure 11), excessive tooth decay and discoloration, lack of mental alertness and listlessness, peripheral neuropathy and gastric disorders. The links with dental health are somewhat equivocal and many of the studies indicating a possible link with selenium failed to take account of other factors such as the fluoride status of the areas of study (WHO, 1987).

Part of the problem in assessing high selenium exposure is that there is some evidence to suggest populations can adapt or tolerate high selenium intakes without showing major clinical symptoms. Investigations are also hampered by the lack of a sensitive biochemical marker of selenium overexposure (WHO, 1996). Hair loss and nail damage are the most common and consistent clinical indications of the condition. Chinese studies carried out in the seleniferous areas of Hubei and Ziyang have demonstrated that these effects are evident above dietary intakes of 900 μg day^{-1}, blood plasma levels of 1 mg L^{-1} and whole blood concentrations of 0.813 mg L^{-1} (Yang et al., 1983). Interestingly, further work in China has shown a marked reduction in the ratio of selenium in plasma compared to that in erythrocytes at dietary intakes of 750 mg kg^{-1}, this is the first indication of a biochemical response to high selenium intakes prior to clinical symptoms developing (Yang et al., 1989). There is still a great deal of uncertainty about harmful doses of selenium but a maximum recommended dietary intake of 400 µg day^{-1} has been proposed based on half the level of intake found in the Chinese studies (WHO, 1996).

IV. Measuring Selenium Status

So far in this chapter we have talked about selenium deficiency and toxicity in the environment, plants, animals and human beings but in order to assess selenium status, it is important to consider how it is measured. Information about the chemical composition of the terrestrial environment is generally collated by national survey organizations concerned with geology, soil, water, agriculture and vegetation. In terms of geology for example, over 100 countries around the world carry out national geochemical mapping programs. These programs are based on systematic collection of materials such as soil, sediment, water, rock and vegetation, which are then analyzed for a range of element compositions and used to produce maps of element distributions in the environment. This type of approach was pioneered in the 1950s by Russian geochemists and the wide application of these methods has been made possible by improvements in rapid multi-element analysis techniques over the last 60 years.

However, selenium is not an easy element to analyze, partly because concentrations in natural materials are so low, therefore, in many multi-element geochemical surveys, selenium was not included in the analysis. It was not until the last 25 years that analytical advances have allowed the detection of selenium at low enough concentrations to be of real interest to environmental studies but because these techniques are more expensive than routine analytical programs, selenium is still often missing from the group of determinants despite its environmental importance (Darnley et al., 1995). A summary of some of the selenium data available around the world is provided by Oldfield (1999).

Analytical methods that give good limits of detection (< 1 mg kg^{-1}) include colorimetry, neuron activation analysis (NAA), X-ray fluorescence spectrometry (XRF), atomic fluorescence spectrometry (AFS), gas chromatography (GC), inductively-coupled mass spectrometry (ICP-MS) and inductively-coupled atomic emission spectrometry (ICP-AES). Of these, AFS is the most widely used for natural materials such as foods, plants and soils. NAA is often used to determine different selenium isotopes, especially in tracer studies using ^{75}Se etc and gives good detection limits but is a more specialized form of analysis. For studying stable isotopes of selenium (for example ^{78}Se and ^{82}Se) ICP-MS may be used but requires enriched and expensive isotope materials. In more recent years, hydride-generation techniques have improved the detection limits of spectrometric methods such as ICP-AES. Ion exchange chromatography has been extensively used to determine selenium compounds in plants whereas gas chromatography is employed to determine volatile selenium compounds. Ion exchange or solvent extraction methods are used to distinguish selenate and selenite species in solution. Recently developed anion exchange high performance liquid chromatography (HPLC) and ICP-dynamic-reaction-cell-MS methods can be used to measure selenium isotopes and selenamino acids including selenocysteine, and selenomethionine. Using these techniques it is now possible to measure relatively low selenium concentrations and selenium element species in a wide variety of environmental and biological materials (WHO, 1987).

In animals and humans a variety of bio-indicators of selenium status have been employed. Due to the close association between the level of dietary selenium intake and GSH-Px activity, the fact that the enzyme activity represents functional selenium and that assessments of this enzyme are easier to perform than selenium tests, GSH-Px activity has been used extensively to measure selenium status, especially in animals. However, this method requires caution because GSH-Px activity is influenced by other physiological factors and a non-selenium-dependent GSH-Px enzyme is also present in animals and humans. Furthermore, the enzyme activity may provide an indication of selenium status at lower levels of intake but at higher concentrations of selenium, the GSH-Px activity becomes saturated and the enzyme cannot be used to indicate toxic selenium status (WHO, 1996).

Other indicators of selenium status include whole blood, plasma or serum, hair, toenail and urine content. Of these, hair has been used extensively as it is easy to collect. However, caution is required to ensure that samples are not contaminated with residues from selenium-containing shampoos. It should also be noted that urinary selenium cannot be used to measure inhalation exposure to hydrogen selenide gas, selenium oxychloride or organic-selenium compounds as severe damage to the lungs occurs before elevated selenium contents are evident in the urine (WHO, 1987). Dietary surveys are also commonly used as an indication of selenium intake, single-day dietary surveys can give errors of up to 90% when used to estimate the real long term exposure to selenium because wide ranges in daily intake are commonplace (0.6 – 221 μg day^{-1}). Comparisons of different methods have shown that three-week dietary observations give estimates of overall intake to within 20% and are a much more reliable indication of likely selenium status (WHO, 1987).

Regardless of the material sampled, whether it is soil, food, blood, water, hair etc. selenium status is determined by comparison to a set of thresholds and normative values that have been determined by examining the levels at which physiological effects occur in plants, animals and humans. Some of these thresholds are listed in Table 18. In general, total soil selenium contents of 0.1 to 0.6 mg kg^{-1} are considered deficient as these are the concentrations of selenium found in regions where selenium-deficient livestock are commonplace such as New Zealand, Denmark and the Atlantic Region of Canada. Work into Keshan disease in China suggests levels of 0.125 mg kg^{-1} total selenium in soil cause selenium deficiency in the food chain (Yang et al., 1983; Yang and Xia, 1995). However, it should be borne in mind that the amount of total selenium in the soil is not necessarily the critical factor determining selenium status. Several studies have demonstrated that the total selenium content of the soil can be considered 'adequate' but if the selenium is not in bioavailable form, it is not taken up into plants and animals and selenium deficiency can result (see for example Fordyce et al., 2000a). Total selenium concentrations in soil can give an indication of likely selenium status but do not necessarily tell the whole story and a selenium deficient environment is not necessarily one in which total concentrations of selenium in soil are lowest. In recent years soil water soluble selenium has been used as an indicator of the bioavailable fraction and Chinese scientists have recommended soil deficiency and toxicity thresholds on this basis, 0.003 and 0.020 mg kg^{-1} respectively (Tan, 1989).

Due to the many different factors that can influence the uptake of selenium from soil into plants, vegetation often provides a better estimate than soil of likely environmental status with regard to health problems in animals and humans. Feed crops containing more than 0.1 mg kg^{-1} selenium will protect livestock from selenium deficiency disorders whereas levels of > 3 - 5 mg kg^{-1} in plants have been shown to induce selenium toxicity in animals (Jacobs, 1989; Levander 1986). 5 mg kg^{-1} is the current MAC of selenium in animal feedstuffs in the USA. In terms of cereal crops for human consumption, Chinese workers suggest deficiency and toxicity thresholds of 0.02 and 0.10 mg kg^{-1} respectively based on epidemiological studies in Keshan disease and selenosis affected areas (Tan, 1989). Determination of the selenium status of water is usually made using comparisons to the WHO maximum admissible concentration of 10 μg L^{-1}.

In veterinary science, concentrations of < 0.04 mg L^{-1} selenium in animal whole-blood are considered deficient and are related to white muscle disease in ruminant species whereas 0.07 – 0.10 mg L^{-1} is considered adequate highlighting the extremely narrow range in selenium status between clinical/non-clinical outcomes (WHO, 1987; Levander 1986). Human selenium status is rather more difficult to categorize because of the lack of overt clinical symptoms in many populations exposed to supposedly deficient or toxic intakes but based on work in China, deficiency and toxicity thresholds in human hair of 0.200 and > 3 mg kg^{-1} (Yang et al., 1983; Yang and Xia, 1995; Tan, 1989) respectively have been suggested whereas dietary limits of 40 and 400 μg day^{-1} are proposed by the WHO as an indication of human selenium status (WHO, 1996).

V. Remediation

A variety of methods have been used to try and counteract the impacts of selenium deficiency and toxicity in environments and within animals and humans as follows.

A. Remediating Selenium Deficiency.

Methods to enhance selenium in the environment and uptake into agricultural crops and animals have been developed over a number of years. One approach is to alter the species of crops grown on deficient soil to plant types that take up more selenium. Switching from white clover production to certain grasses has been used successfully in New Zealand to increase the selenium content of fodder crops (Davis and Watkinson, 1966). Another approach is to apply selenium-rich fertilizers to the soil to increase the amount of selenium being taken up by plants, animals and humans. Some rock phosphate fertilizers are rich in selenium and can be used to enhance uptake, however, there is some risk associated with application of selenates to alkali and neutral soils because of high bioavailability. Use of selenate fertilizer results in much higher selenium contents of first cuts of crops or forage, which decrease sharply with subsequent cropping. Addition of selenite to acid-neutral soils can result in some loss of selenium to soil adsorption therefore decreasing the effectiveness of the application, but in some cases this mechanism can ensure that levels of uptake are not toxic (Jacobs, 1989; Fleming, 1980). The selenium concentration of foods can also be increased by supplementing ordinary fertilizers with soluble selenium compounds. At the current time, only Finland, New Zealand and parts of Canada and China allow selenium-enhanced fertilizers to be used for the cultivation of food crops, these countries use fertilizers based on sodium selenate (Oldfield, 1999). For example, in New Zealand 1% granular selenium is mixed with granulated fertilizer and is applied at a rate of 10 g Se ha^{-1} over about a quarter of the agricultural land in the country (in 1998 1.2 million of 4.5 million ha underwent selenium-fertilization) (Jacobs, 1989; Oldfield, 1999).

Problems of uptake associated with retention of selenium in the soil can be circumvented by direct application of the fertilizer to the plants themselves. Foliar application of selenite to plants has been successfully used to increase the selenium content of crops and animals. Spraying selenium at 3 – 5 g ha^{-1} has been shown to increase the content in grain whereas sodium selenite applied at 50 – 200 g Se ha^{-1} maintained > 0.1 mg kg^{-1} contents in crops through three harvests. Studies have shown that the selenium content of crops is enhanced by mid-tillering spraying with selenium fertilizer but cannot be applied successfully to seeds (Jacobs,1989).

For example, Chinese workers have reported much better uptake of selenium in maize crops, grown on aerated oxygenated soils than in rice grown in the same soils under water-logged conditions due to reduction of selenium to insoluble forms. To avoid poor uptake of selenium from soils as a consequence of the waterlogged conditions, foliar spraying of sodium selenite at an early shooting stage of the rice plant growth was found to improve the selenium content of the grain and hull Cao et al., (2000). In another study, the average wheat selenium contents in Kashin Beck endemic areas were 0.009 mg kg^{-1} dry weight resulting in daily intakes of 12 µg in the local population. Following foliar selenium fertilizer application, wheat contents increased to 0.081 mg kg^{-1} dry weight and human daily dietary intakes rose to 47 µg (Tan et al., 1999).

In Finland, the bioavailability of soil selenium for plants is generally poor owing to the relatively low selenium concentration, low pH and high iron content of the soil as much of the country comprises very ancient hard crystalline granite and gneiss rocks, very similar to Eastern Canada where selenium supplementation is also practiced (Jacobs, 1989). In 1984, the Finnish government approved a program of selenium supplementation in fodder and food crops. The program initially involved spraying a 1% selenium solution onto fertilizer granules giving an application rate of 6 g Se ha^{-1} for silage and 16 g ha^{-1} for cereal crops. Within two years a three-fold increase of mean selenium intake in the human population was observed and human serum contents increased by 70%. The supplementation affected the selenium content of all major food groups with the exception of fish. In 1990 the amount of selenium that was supplemented was reduced to 6 g Se ha^{-1} for all crops and the mean human selenium intake fell by 30% and the serum selenium concentration decreased by 25% from the highest levels observed in 1989. According to data obtained, supplementation of fertilizers with selenium is a safe and effective means of increasing the selenium intake of both animals and humans and is feasible in countries like Finland with relatively uniform geochemical conditions (Aro et al.,1995). In other countries were the low level of selenium intake is currently of concern, such as the UK, this kind of intervention would require careful planning and monitoring of the effects on both animal and human nutrition and the environment because geochemical conditions vary markedly across the country as a result of a diverse geological environment.

In addition to attempts to enhance selenium in fodder crops and animal feeds supplemented with sodium selenite or selenate, selenium deficiency in animals is also prevented by veterinary interventions such as selenium injections to females during late gestation and/or to the young stock shortly after birth, dietary supplements, salt licks and drenches (Levander, 1986).

In humans also, direct dietary supplementation methods have been used successfully to counteract selenium deficiency. Pills containing selenium alone or in combination with vitamins and/or minerals, are available in several countries. Selenium supplements contain selenium in different chemical forms. In the majority of supplements, the selenium is present as 35 selenomethionine, however, in multivitamin preparations, infant formulas, protein mixes and weight-loss products, sodium selenite and sodium selenate are predominantly used. In other products, selenium is present in protein- or amino acid chelated forms. Current animals studies and epidemiological evidence favors selenomethionine as the most bioavailable and readily taken up form of selenium in mineral supplements. A dosage of 200-µg day^{-1} is generally considered safe and adequate for adults of average weight consuming a North American diet (WHO, 1987). Studies carried out in Keshan disease areas of China have shown that both selenite and selenium-yeast supplements were effective in raising GSH-Px activity of selenium-deficient populations but selenium-yeast provided a longer lasting body pool of selenium (Alfthan et al., 2000). Altering the diets of humans to include selenium-rich foods has also proved successful in preventing selenium deficiency. In China, selenium rich tea, mineral water and cereal crops are now marketed in selenium deficient areas.

B. Remediating Selenium Toxicity.

One of the most common methods to reduce the effects of selenium in soil is phytoremediation. This practice is carried out by growing plant species, which accumulate selenium from the soil and volatilize it to the air to reduce levels in soil. For example, the hybrid polar trees *Populis tremula x alba* can transfer significant quantities of selenium by volatilization from soil to air, the rate for selenomethionine is 230 times that of selenite and 1.5 times higher for selenite than selenate. These trees have been used successfully to reduce selenium contents in soil in the Western USA (Oldfield, 1999).

There is some evidence to suggest that the presence of phosphate and sulfate in soils can inhibit the uptake of selenium in plants and application of these minerals as soil treatments could be beneficial against selenium toxicity in agricultural crops. Studies have shown a 10-fold increase in sulfate content reduced uptake from selenate by > 90% in ryegrass and clover whereas a similar increase in phosphate content caused 30% - 50% decreases in selenium accumulation from selenite in ryegrass, but in clover such decreases only occurred in the roots. Therefore, sulfate-selenate antagonisms were much stronger than phosphate-selenite antagonisms. The addition of sulfur or barium sulfate (gypsum) to seleniferous soils in North America was not successful in reducing uptake into plants probably because these soils already contain high quantities of gypsum, however, additions of calcium sulfate and barium chloride have been shown to markedly reduce the uptake of selenium in alfalfa in the USA (90 – 100 %) probably due to the formation of $BaSeO_4$ which is barely soluble. However, the practicalities of this type of selenium remediation method are rather limited (Jacobs, 1989).

It is more common to counteract selenium toxicity with veterinary and medical interventions. Sodium sulfate and high protein intakes have been shown to reduce the toxicity of selenate to rats but not of selenite or selenomethionine in wheat. Arsenic, silver, mercury, copper and cadmium have all been shown to decrease the toxicity of selenium to laboratory animals and have been used to alleviate selenium poisoning in dogs, pigs, chicks and cattle (WHO, 1987; Levander, 1986; Moxon, 1938). The protective effect of arsenic is thought to be a consequence of increased biliary selenium excretion. Laboratory evidence suggests that mercury, copper and cadmium exert a beneficial effect due to reactions with selenium in the intestinal tract to form insoluble selenium compounds. However, consideration must be given to the toxic effects of these elements before they are applied as selenium prophylaxis. Linseed meal has also been found to counter selenium toxicity in animals by the formation of selenocyanates, which are excreted (WHO, 1987).

In terms of human diets, dietary diversification can also help reduce selenium toxicity, in China, high-selenium cereal crops are banned from local consumption and exported out of the seleniferous regions where they are mixed with grains from elsewhere before sale in selenium-deficient parts of the country.

VI. Case Histories

A. Selenium Toxicity in Animals – Kesterson Reservoir, USA.

One of the best-known and most studied incidences of selenium toxicity in animals has been recorded at Kesterson Reservoir, California, USA. The information summarized here is taken from Jacobs (1989); Wu et al. (2000); Wu (1994) and Tokunaga et al. (1996), publications that should be referred to for further details.

Due to a scarcity of wetlands in California, wildlife resource managers tried using irrigation run-off from sub-surface agricultural drains to create and maintain wetland habitats at the Kesterson Reservoir. The reservoir comprises 12 shallow ponds acting as evaporation and storage basins for agricultural drain waters from the San Joaquin Valley. During part of the year, the water from the reservoir was to be discharged via the San Luis drain back into the Sacramento-San Joaquin River Delta when river flows were high enough to dilute the contaminants present in the agricultural water. However, construction of the San Luis drain was halted in 1975 due to increased environmental concerns about the impact of the drain water on the river delta. During the 1970s surface water flow into the reservoir predominated but into the 1980s almost all the flow was shallow subsurface agricultural drainage water. Selenium concentrations in agricultural drainage water entering the Kesterson Reservoir area between 1983 and 1985 were 300 mg L^{-1} as a result of contact with seleniferous soils in the catchment area. In this arid alkaline environment, 98% of the selenium was in the most readily bioavailable selenate form with only 2% present as selenite. The effects of this water on plants and animals were relatively unknown prior to studies carried out between 1983 and 1985 by the USA Wildlife Service comparing Kesterson to the adjacent Volta Wildlife area, which was supplied with clean irrigation water with normal concentrations of selenium. The mortality of embryos, young and adult birds, survival of chicks and embryonic deformities were compared between the two sites. The selenium content of the livers of snakes and frogs from the two areas were also examined in addition to tissues from 332 mammals of 10 species, primarily moles. Results of some of the comparisons between biota from the two sites are shown in Table 19. In all cases, the levels of selenium in biological materials at Kesterson Reservoir exceeded those of the Volta Wildlife area several-fold. Concentrations of selenium in water were compared to those in biota collected from the same site and bioaccumulation factors of more than 1000 for animals were found at Kesterson. Although no overt adverse health effects were noted in reptile or mammal species such as voles and raccoons in the area, the levels of selenium present were of concern in terms of bioaccumulation in the food chain. In contrast, the overt health effects on birds were very marked with 22% of eggs containing dead or deformed embryos as a result of selenium toxicity. The developmental deformities included missing or abnormal eyes, beaks, wings, legs and feet and hydrocephaly and were fatal. It is estimated that at least 1000 adult and juvenile birds died at Kesterson in the period 1983 – 1985 as a result of consuming plants and fish with 12 – 120 times the normal amount of selenium (Jacobs, 1989).

Following these revelations, Kesterson Reservoir was closed and a series of remedial measures were tested by a team of scientists who were able to provide a more thorough understanding of processes leading to selenium transport and biologic exposure in this environment. Some of the schemes proposed included the development of an in situ chemical treatment to immobilize soluble selenium in drained evaporation pond sediments by amendment with ferrous iron, which occludes selenate and selenite in ferric oxyhydroxide (FeOOH). Phytoremediation techniques were also tested. These included the growing of barley (*Hordeum vulgare L.*) and addition of straw to the soil, which contained 0.68 mg kg^{-1} soluble selenium and 6.15 mg kg^{-1} total selenium. Four treatments were evaluated: soil only, soil + straw, soil + barley, and soil + straw + barley. At the end of the experiments, selenium in barley represented 0.1-0.7% of the total selenium in the system, and volatilized selenium accounted for 0.2 to 0.5% of total selenium present. In contrast, straw amendments were found to greatly reduce the amount of selenium in soil solution by 92-97% of the initial soluble selenium and represented a possible remediation strategy for the

Reservoir. The planting of canola (*Brassica napus*) was also evaluated but accumulated 50 mg kg^{-1} (dry weight), which accounted for less than 10% of total selenium lost in the soil solution during the post-harvest period.

Bioremediation through the microbial reduction of toxic oxyanions selenite and selenate into insoluble Se^0 or methylation of these species to dimethylselenide was proposed as a potential bioremediation cleanup strategy. Field trials demonstrated that microorganisms, particularly *Enterobacter cloacea*, were very active in the reduction of selenium oxyanions present in irrigation drainage water, into insoluble Se^0 and, by monitoring various environmental conditions and the addition of organic amendments, the process could be stimulated many times. Based upon the promising results of these studies, a biotechnology prototype was developed for the cleanup of polluted sediments and water at Kesterson.

A soil excavation plan had been proposed to remove selenium contaminated material from the site, however, extensive monitoring of pore water in the vadose zone* demonstrated that this plan would be ineffective in reducing the elevated selenium concentration in ephemeral pools present during the winter at Kesterson. Furthermore, extensive biological monitoring demonstrated that selenium concentrations in the dominant species of upland vegetation at Kesterson were near or equal to "safe" levels.

On the basis of these studies, a cost-effective remediation strategy was devised. Firstly, the groundwater under Kesterson was protected from selenium contamination by naturally occurring biogeochemical immobilization. Secondly the contaminated soil and sediment was left in place but low-lying areas were in filled to prevent the formation of the ephemeral pools that attracted wildlife. The area was then planted over with upland grassland species. Monitoring studies carried out on soil and vegetation between 1989 and 1999 showed that selenium losses from soil via volatilization were approximately 1.1% per year. Soil selenium concentrations in the fresh soil fill sites increased in the top 15 cm indicating that the plants were able to effectively take up soluble soil selenium from the lower soil profile and deposit it at the land surface thus reducing the rate of leaching of soil selenium. In general plant tissue concentrations reflected the amount of soil water-soluble selenium present, which was low. In 1999 plant tissue concentrations averaged 10 mg kg^{-1} (dry weight) and soil water-soluble selenium contents 110 mg kg^{-1} giving an estimated bioaccumulation value for the upland grassland of less than 10% of the previous wetland habitat. It was concluded that the new Kesterson grassland did not pose a risk to the environment (Wu et al., 2000).

B. Selenium Toxicity and Drinking Water – Reggio, Italy.

Examples of high selenium exposure related to intakes in water are very scarce. An exception is reported by Vinceti et al. (1998) and occurred in the town of Reggio, Italy between 1972 – 1988 where the population in the Rivalta neighborhood were inadvertently exposed to wells containing 3 – 13 μg L^{-1} selenium as selenate and resultant tap water containing 7 – 9 μg L^{-1} compared to selenium contents in the drinking water of adjacent neighborhoods of < 1 μg L^{-1}. The wells were closed off in 1989 and the population are no longer exposed to water from this source. Apart from the selenium content, water quality between Rivalta and the other neighborhoods was the same. Using residency and water supply records, 2065 people (1021 men and

1044 women) were identified as having been exposed for at least 11 years to the elevated selenium content in the water between 1975 and 1988, this cohort was compared to a control population of non-exposed individuals from the same town. To examine the effects of this exposure on cancer incidence in the local population, all cases of pathologically confirmed primary invasive melanoma occurring during 1996 were collated for the entire town of Reggio as well as records on age, sex, educational level and occupation. The exposed and non-exposed populations had similar educational and occupational profiles and once the data were corrected for age and sex, a higher prevalence of skin cancer was noted in the exposed population. On the basis of melanoma rates in the unexposed population 2.06 cases would be expected in the exposed population whereas 8 cases were reported. Although other co founding factors could not be taken into account in this study, there is some evidence to suggest that the skin is a target organism in chronic selenium toxicity and that inorganic selenium can act as a pro-oxidant and mutagen and cell apoptosis suppressant which may account for the higher prevalence of cancer in the exposed group. It should be noted that selenium is ineffective against melanoma although beneficial for other forms of cancer (Clark et al. 1996).

C. Selenium Deficiency in Humans – Zhangjiakou District, Hebei Province, China.

Zhangjiakou District, Hebei Province in China lies between Inner Mongolia to the north and Beijing to the south and is one of the remotest regions of China lying within the northeast-southwest Keshan disease (KD) belt (Figure 8). The area is underlain by Archaen metamorphic* and Jurassic volcanic rocks, which are overlain by Quaternary loess and alluvial deposits, all of which contain low amounts of selenium. Within

Zhangjiakou District, the KD belt follows the mountainous watershed between the two rock types reflecting the fact that villages in the remotest locations where populations are most dependent on locally grown foodstuffs, are most at risk from the disease. However, within the KD belt, prevalence rates show marked variability between villages ranging from 0 – 10.8 % between 1992 and1996. In a study to examine why this variation may occur and to pinpoint more exactly the relationships between environmental selenium and disease, Johnson et al. (2000) examined soil, staple crop (wheat and oats), water and human hair selenium levels in 15 villages in the region classified according to disease prevalence into three groups – no KD 0% prevalence, moderate KD 0 – 3% prevalence and high KD - > 3% prevalence. Results showed that hair, grain and water selenium concentrations showed an inverse relationship with disease prevalence as expected, the highest selenium contents were reported in villages with lowest prevalence of the disease. However, contrary to expectations, soil total selenium contents showed the opposite relationship and were highest in the villages with greatest disease prevalence (Figure 12). Indeed comparisons between the data collected from high prevalence villages for the study and selenium deficiency thresholds proposed by Tan (1989) indicated that the selenium contents of all sample types were very low but whilst hair (geometric mean 177 ng g^{-1} – threshold 200 ng g^{-1}) and grain (geometric mean 7.8 ng g^{-1} – threshold 25 ng g^{-1}) contents would be classed as deficient, soil total selenium contents would not (geometric mean 171 ng g^{-1} – threshold 125 ng g^{-1}). There was a strong correlation between the selenium content of grain and the selenium status of the local population determined by hair sampling but relationships with local soils were less clear. Further examinations into the soil geochemistry demonstrated that soils in the high KD prevalence villages were black or dark brown with a high organic matter content and lower pH than other soils in the region. Although these soils contained high total selenium contents it was not in a readily bioavailable form as it was held in the organic matter in the soil. Despite the higher total selenium contents, water soluble selenium in the high prevalence villages were in fact lower than deficiency threshold values (geometric mean 0.06 ng g^{-1} – threshold 3 ng g^{-1}). This study concluded that when environmental concentrations of selenium are low, any factor that is responsible for reducing the mobility of selenium may have a critical effect and emphasizes the importance of determining the bioavailability of selenium rather than the total selenium content when assessing impacts on human health. On the basis of this study, conditioning treatments to raise the soil pH thus increasing the bioavailability of selenium in the organic rich soils or foliar application of selenium fertilizer to crops to avoid selenium adsorption in the soils were recommended as remediation strategies to increase the levels of selenium in local diets. The study also demonstrates the importance of understanding the biogeochemical environment in the determination of selenium deficient regions and appropriate remediation techniques. However, here as with elsewhere in China, no incidences of the KD have been reported in the area since 1996 as economic and communication improvements diversify the diet and enhance the health of the population.

D. The Geological Impact of Selenium on Human Health –Deficiency and Toxicity, Enshi District, Hubei Province, China.

If there is one place on Earth that demonstrates the importance of geological controls on selenium and human health it is Enshi District, Hubei Province in China, which lies approximately 100 km south of the Yangtze River Gorges and 450 km west-south-west of the provincial capital Wuhan (Figure 8). In Enshi District, selenium-deficiency related diseases (Keshan disease) and selenium, toxicity (selenosis) occur within 20 km of each other, their incidence being controlled by geology. The area is very mountainous with little connectivity between villages some of which can only be reached on foot, hence populations are very dependent on the local environment for their food supply.

Jurassic sandstones, which contain low concentrations of trace elements including selenium, underlie the northwest of Enshi District and Keshan disease (KD) is present in this area. Selenium toxicity, on the other hand, is associated with high environmental selenium derived from Permian age coal-bearing strata in the center and east of Enshi District. Soils developed over Jurassic sandstones comprise red-purple sands whereas light-brown silts and clays containing many carbonaceous fragments are typical in areas underlain by the Permian strata.

Studies into the selenium balance of local populations were carried out during the 1960s and 1970s by Enshi Public Health Department in response to outbreaks of selenium-related diseases in the area. Between 1923 and 1988, 477 cases of human selenosis were reported. 338 of these cases, resulting in hair and nail loss and disorders of the nervous system, occurred between 1959 and 1963 in Shadi, Xin Tang and Shuang He communities. In Yu Tang Ba village, Shuang He community, the population was evacuated after 82% (19 out of 23 people) suffered nail and hair loss and all livestock died from selenium poisoning. During the same period, 281 selenosis cases were reported in five villages in the Shadi area. Cases of selenosis in pigs reached peak prevalence between 1979 and 1987 when 280 out of 2238 animals were affected in Shatou resulting in 122 deaths. No human cases of selenium toxicity have been reported in recent years but animals commonly suffer hoof and hair loss as a result of the high environmental selenium.

During the late 1960s and 1970s, an area of selenium deficiency in Lichuan County to the northwest of Enshi District was also identified and lies within the KD belt across China. In total, 312 people have suffered KD in the County, an average incidence rate of 103 per 100 000. Among the 312 cases, 136 recovered, 163 died and 13 persons still suffer from the disease. The village of Chang Ping was the worst affected with a total of 259 cases out of a population of 20368 and 117 of those affected died. Children between the ages of 3 - 8 accounted for 83.4% of the total cases and 80% of the children affected by the disease died. Following peak prevalence in 1969 (106 cases), the number of cases has fallen dramatically and current prevalence rates are unknown as no medical investigations have been carried out in recent years.

Yang et al. (1983) were the first to compare levels of selenium in soil, crops, drinking water, human urine, blood, nail and hair samples from the Enshi area with other regions of China and demonstrate that the endemic selenium intoxication of humans in Enshi was related to the occurrence of Permian selenium-enriched shaley coal, which contains up to 6471 mg kg^{-1} selenium. There is some evidence to suggest that selenium in these rocks is in the form of micro particles of elemental selenium in association with organic carbon and that the carbon content of the rock controls the selenium content. However, some selenium is also found in the lattice of pyrite minerals. Selenium concentrations in soil, food and human samples from areas underlain by carbonaceous strata were up to 1000 times higher than in samples from selenium-deficient areas where KD was prevalent and dietary intakes of selenium greatly exceed the USA National Research Council and Chinese recommended standards (Table 20). It was estimated that locally grown crops constituted 90% of the diet in the Enshi area and cereal crops (rice and maize) accounted for 65 - 85% of the selenium intake indicating the importance of the local environment to selenium in the food chain. In addition to exposure via soils and foodstuffs, villagers in the selenosis region also mine the carbonaceous shale for fuel and use burnt coal residues as a soil conditioner. Although the epidemiological investigations revealed that selenosis occurred in areas of high environmental selenium associated with the carbonaceous strata but not all villages underlain by this strata were affected.

Further studies carried out by Fordyce et al. (2000b) into three groups of villages, one suffering KD, one with high environmental selenium but no selenosis and one with high environmental selenium and selenosis showed that in the high-selenium villages, concentrations of selenium in soils and foodstuffs could vary markedly from low to toxic within the same village, these variations being dependent on the outcrop of the coal-bearing strata. The wide range in geochemical conditions could in part explain why some villages suffered selenosis and others did not. Villagers were therefore advised to avoid cultivating fields underlain by the coal and were counseled against using coal-derived products, such as ash, to condition the soil. In the KD affected villages of Lichuan County, selenium concentrations in staple food crops (rice and maize), drinking water and the human populations (measured in hair samples) were very low and soils in this area had lower pH contents than soils in the high-selenium villages, which would further inhibit the uptake of selenium into plants. Conditioning the soil with lime to increase the pH making selenium more mobile was suggested as a remediation strategy.

Although all the villages in the low selenium area had marginal –deficient selenium status and the majority of villages in the high-selenium area had excessive amounts of selenium in the environment and human population using the thresholds defined by Tan (1989) (Table 21), no new incidents of either KD or overt selenium poisoning have occurred in recent years. This suggests that the local population may have adapted to the high and low selenium intakes present in the different environments and that the historical occurrences of clinical effects related to selenium imbalances were caused by other factors. The outbreaks of human selenosis in Enshi during the late 1950s and early 1960s coincided with a drought and the failure of the rice crop. The crop failure had serious implications for the dietary intake and health of the local population with less food available, reduced protein intake and higher dependence on vegetables and maize and natural plants. These factors may have lead to the severe outbreaks of selenosis in the Enshi area and demonstrate that in geologically controlled high or low selenium environments additional stresses can lead to serious health outcomes in the local population.

E. The Geological Impact of Selenium on Animal Health –Deficiency and Toxicity, Queensland, Australia.

Another example of the effects of geology on selenium and health has been reported in Queensland, Australia. Here seleniferous limestones and shales of the Tambo Formation cause selenium toxicity symptoms in livestock grazing plants in this area whereas less than 100 km to the south selenium deficiency and white muscle disease in grazing animals is a problem over Tertiary Volcanic soils. Grain grown over the seleniferous limestone rocks contains > 0.2 mg kg^{-1} selenium whereas over the southern selenium deficient region concentrations rarely exceed 0 – 0.05 mg kg^{-1} in grain (Oldfield, 1999). This is another example of how geologically controlled geochemical variation can influence selenium status and health over relatively short distances.

F. Selenium Status in Western Countries – Is Environment Still Important?

With the exception of Italy, so far the human case studies presented in this Chapter refer to developing countries where populations are very dependent on the local environment to provide the correct mineral balance. Under these circumstances it is easy to see why considerations of selenium status may be important. But what of the western world where people generally move around more during their lifetimes, products are derived from all around the world and people buy food in large supermarkets rather than growing it in their own back yard? Under these conditions, the links between environment and health are less direct. Nonetheless, the impact of the selenium status of the environment on animals and humans is still evident. It has already been pointed out in this chapter that New Zealand is a generally selenium-deficient country compared to other areas of the world, indeed cereal grains grown in New Zealand contain 10 times less selenium than grain from Canada and the USA. In years when the crops in New Zealand are poor, wheat is imported from Australia and a corresponding notable increase in blood selenium levels are seen in the population. Studies have also shown that the average total body contents of selenium are only 3 – 6.1 mg kg^{-1} in New Zealand compared to14.6 mg kg^{-1} in the USA and studies into individual tissues of the body show that in New Zealand, concentrations are half that of the USA. A marked lowering of blood selenium levels has been noted in populations moving from selenium adequate areas of the USA to New Zealand, however, the actual resultant values also depend on factors such as physiological status (WHO, 1987). There is clear evidence therefore of the influence of the geochemical environment on food and human selenium status when either food or people move from one area to another. But what of within country variation? Perhaps the most compelling evidence that environmental differences are important even within western countries comes from the USA where despite one of the most diverse and mobile food-supply chains in the world selenium concentrations in animals and humans reflect the surrounding environment. Studies have shown that despite the widespread use of agricultural management practices including selenium supplementation, the selenium content of skeletal muscle in cattle shows marked geographic variation concordant with selenium contents in soils and grasses and perhaps even more surprisingly, human blood selenium levels are higher in the seleniferous western US than in selenium poor areas, for example serum selenium contents average 0.161 $\mu g\ L^{-1}$ in Ohio compared to 0.265 $\mu g\ L^{-1}$ in South Dakota (WHO, 1987). Hence, even in populations who now live one step removed from their natural environment, the cycling of selenium from nature into humans is still of fundamental importance to health.

VII. Future Considerations

This chapter has demonstrated that human exposure to the biologically important element selenium is largely dependent on dietary intakes in food and water, which are significantly controlled by variations in the geology of the Earth’s surface. Although much work has been done over the past 30 years to enhance our understanding of environmental selenium, over large areas of the globe information is still missing because until recently selenium was a difficult element to analyze. More work is required to understand not just the total amounts of selenium present but also the bioavailability of the element and cycling through the environment. For example, it is only recently that the importance of the oceans in the cycling of selenium has been recognized. The selenium status of the human and animal populations around the globe closely reflect environmental levels and although overt clinical symptoms of selenium toxicity and deficiency are rarely reported, the possible sub-clinical effects and implications of selenium status are at present poorly understood and should not be under estimated as medical science continues to uncover new essential functions for the element. In the future, closer collaboration between medical and environmental scientists will be required to evaluate the real environmental health impact of this remarkable element in diseases such as cancer, AIDS and heart disease.

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