

The Summer Meeting of the Nutrition Society was held at the University of Surrey, Guildford on 30 June–2 July 2009

## Conference on ‘Over- and undernutrition: challenges and approaches’

### Symposium on ‘Geographical and geological influences on nutrition’ Factors controlling the distribution of selenium in the environment and their impact on health and nutrition

Christopher C. Johnson<sup>1\*</sup>, Fiona M. Fordyce<sup>2</sup> and Margaret P. Rayman<sup>3</sup>

<sup>1</sup>British Geological Survey, Keyworth, Nottingham NG12 5GG, UK

<sup>2</sup>British Geological Survey, Murchison House, West Mains Road, Edinburgh EH9 3LA, UK

<sup>3</sup>Nutritional Sciences Division, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK

Se is essential to human and animal health but can be toxic in excess. An interest in its geochemistry has developed alongside a greater understanding of its function in a number of health conditions. Geology exerts a strong control on the Se status of the surface environment; low-Se rock-types (0.05–0.09 mg Se/kg) make up the majority of rocks occurring at the Earth’s surface, which in turn account for the generally low levels of Se in most soils. However, there are exceptions such as associations with sulfide mineralisation and in some types of sedimentary rocks (e.g. black shales) in which contents of Se can be much higher. Baseline geochemical data now enable a comparison to be made between environmental and human Se status, although a direct link is only likely to be seen if the population is dependent on the local environment for sustenance. This situation is demonstrated with an example from the work of the British Geological Survey in the Se-deficiency belt of China. The recent fall in the daily dietary Se intake in the UK is discussed in the context of human Se status and declining use of North American wheat in bread making. Generally, US wheat has ten times more Se than UK wheat, attributed to the fact that soils from the wheat-growing belt of America are more enriched in Se to a similar order of magnitude. In agriculture effective biofortification of crops with Se-rich fertilisers must be demonstrably safe to the environment and monitored appropriately and baseline geochemical data will enable this process to be done with confidence.

#### Environmental Se: Human Se status: Se deficiency in China: Se intake in UK

Se is an element essential to human and animal health in trace amounts but is harmful in excess. It is the toxic effects of excess Se that first brought attention to the health impacts of this element<sup>(1,2)</sup>, i.e. selenosis in human subjects and blind staggers and alkali disease in livestock. Even before the symptoms were attributed to Se poisoning there are historical references to the toxic effects of Se on livestock. Pedro Simon, a 16th century missionary, recorded that in areas of Columbia farm animals suffered from hair loss and other abnormalities<sup>(3)</sup>. Approximately 400 years later the cause was attributed to poisoning by Se taken up by plants in seleniferous soils<sup>(4)</sup>. Even earlier in the 13th century there are apocryphal tales of Marco Polo’s horses

suffering from lost hair and hooves in ancient Suzhou of western China, again attributed to Se poisoning. However, recent research concludes that whilst suffering symptoms similar to Se poisoning, the ailment of the horses recorded by Marco Polo in 1295 might not have been selenosis<sup>(5)</sup>.

Literature on the role of Se as an essential trace element was published in the 1950s<sup>(6)</sup>, although it is really in the last few decades that there has been a substantial increase in research into the health impacts of Se deficiency. This research has been catalysed by certain key medical investigations such as the discovery in 1971 that glutathione peroxidase is a selenoenzyme<sup>(7)</sup> and the landmark clinical trial that appears to show that Se can reduce the risk of

**Abbreviations:** BGS, British Geological Survey; KD, Keshan disease.

**\*Corresponding author:** Dr Christopher C. Johnson, fax +44 1159 363 200, email ccj@bgs.ac.uk

**Table 1.** Industrial uses of selenium (after Fordyce<sup>(15)</sup>)

Industry	% total production used by US industry in 1985
Electrical components (semi-conductors, cables and contacts); photocopier manufacture	35
Glass manufacture	30
Photographic emulsions, printing and graphics; pigments in plastics, paints, enamels, inks, rubber, textiles; pharmaceutical catalyst; additive to petroleum fuel and lubricant products; accelerator and vulcanising agent in rubber manufacture	25
Metal alloys; fungicides; pesticides; nutritional additive to livestock feed; anti-dandruff shampoo; medical applications	10

cancer<sup>(8)</sup>. A range of health conditions relating to Se intake are considered elsewhere<sup>(9)</sup> and are discussed later in the present paper.

The study of the behaviour and distribution of chemical elements in the Earth is a subdiscipline of geology referred to as geochemistry. Eleven elements (Al, Ca, Fe, K, Mg, Mn, Na, O, P, Si and Ti) are described as major elements as they form >99% (w/w) of most rocks. All other elements are generally less abundant and when concentrations are <1000 mg/kg they are described as trace elements. Se is considered to be a trace element, placed 70th in abundance of the list of eighty-eight naturally-occurring elements in the Earth's crust<sup>(10)</sup>. The interest in Se as an essential trace element in the human diet, as well as its potential to be toxic in Se-rich areas, has increased the interest in Se geochemistry and this position is reflected in the many texts that discuss Se in the environment (for example, see Thorton *et al.*<sup>(11)</sup>, McNeal & Balistreri<sup>(12)</sup>, Haygarth<sup>(13)</sup>, Plant *et al.*<sup>(14)</sup> and Fordyce<sup>(15)</sup>).

A better knowledge of the distribution of Se in the surface environment facilitates an understanding of its possible impact on human and animal nutrition and health. In particular, an understanding of the physico-chemical properties that control the movement of Se in the food chain (e.g. soil pH, organic content and speciation) enable a better prediction of potential risks from Se deficiency and toxicity. In the late 1990s a number of case studies in Se-deficient and Se-toxic areas of China were conducted by the British Geological Survey (BGS), in collaboration with scientists from the Chinese Institute of Rock and Mineral Analysis. These studies were carried out in remote areas in which a good connection could be made with human health and the local environment on which the local population were very dependent for their food and water supplies. Results from the Zhangjiakou District of China<sup>(16)</sup> are summarised here as a way of illustrating the factors that control Se in the surface environment and how the environmental Se status relates to human Se status.

### Geochemistry of selenium

Since its discovery in 1817 by Jons Jakob Berzelius Se has been an element that has attracted little attention and study by geochemists. As its concentrations in most geological materials are very low it has been difficult to study its distribution at the Earth's surface. It was Se toxicity in the environment that first attracted substantial attention to Se geochemistry and at about the same time, in the 1930s,

industrial uses for Se began to develop (e.g. invention of the photocopier and Se rectifiers), driving a demand for Se as a commodity (Table 1).

With the improvement in analytical methodology in recent years low levels of Se can more easily be determined routinely in geological and other environmental samples. For example, using X-ray fluorescence spectrometry, particularly X-ray fluorescence energy dispersive spectrometry, the BGS now routinely produces regional maps of Se in soils and stream sediments based on the analysis of thousands of samples (e.g. Wales geochemical atlas<sup>(17)</sup> and Fig. 1).

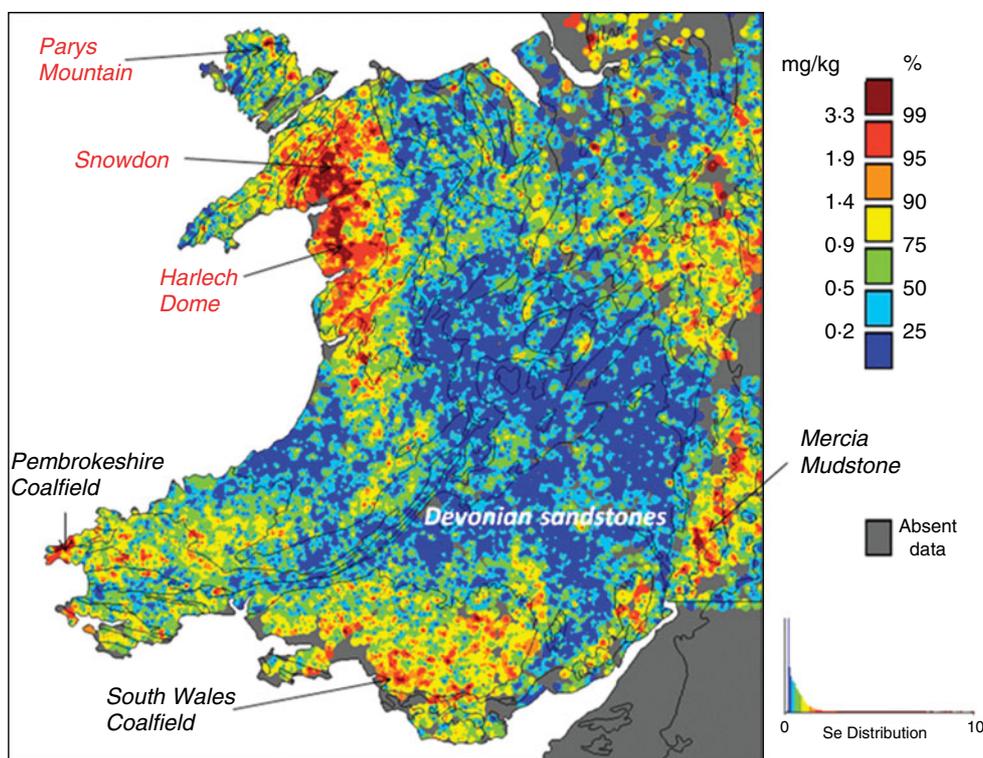
### Chemical properties and production

Se (atomic number 34, atomic mass 78.96 and period group 16) has chemical and physical properties that are intermediate between those of metals and non-metals. In its chemical behaviour it resembles S and exists in similar oxidation states (see Table 2). The oxidation state of Se is critical in determining its availability in the food chain. For example, in neutral-to-alkaline soils Se<sup>6+</sup> (selenate) is the dominant species. This form of Se is generally more soluble and mobile in soils and is readily available for plant uptake. Selenite (Se<sup>4+</sup>) has lower solubility and a greater affinity for adsorption on soil particle surfaces than Se<sup>6+</sup> and hence selenites are less bioavailable in agricultural crops<sup>(18)</sup>.

There are no mines in the world that specifically extract Se; instead it is a by-product of the production of other metals (e.g. refining of Pb and Cu) or recovered from the sludge accumulated in H<sub>2</sub>SO<sub>4</sub> plants.

### Distribution and cycling

As rocks and minerals at the Earth's surface are the primary source of Se in the terrestrial environment, knowing its natural abundance in these sources is important to understanding Se distribution. Average crustal abundances of Se are generally very low (0.05–0.09 mg/kg)<sup>(19)</sup>. Intrusive igneous rocks, e.g. granites, rarely exceed these concentrations. For extrusive (volcanic) rocks Se concentrations are more complex. Ash and gases associated with volcanic activity can contain substantial quantities of Se<sup>(20)</sup> but this process leaves behind volcanic rocks such as basalts and rhyolites that have relatively very low concentrations of Se<sup>(21–24)</sup>. Generally, sedimentary rocks are richer in Se than are igneous rocks but limestones and sandstones will rarely contain >0.1 mg/kg<sup>(24)</sup>. As it is estimated that



**Fig. 1.** Distribution of selenium in drainage sediments from Wales (British Geological Survey<sup>(17)</sup>). This map is based on 19 000 stream-sediment samples collected at a density of approximately one sample per 1.5 km<sup>2</sup> as part of the British Geological Survey's Geochemical Baseline Survey of the Environment project.

**Table 2.** Chemical forms of selenium in the environment (after Fordyce<sup>(15)</sup>)

Oxidative state	Chemical forms
Se <sup>2-</sup>	Selenide (Se <sup>2-</sup> , HSe <sup>-</sup> , H <sub>2</sub> Se <sub>aq</sub> )
Se <sup>0</sup>	Elemental selenium (Se <sup>0</sup> )
Se <sup>4+</sup>	Selenite (SeO <sub>3</sub> <sup>2-</sup> , HSeO <sub>3</sub> <sup>2-</sup> , H <sub>2</sub> SeO <sub>3aq</sub> )
Se <sup>6+</sup>	Selenate (SeO <sub>4</sub> <sup>2-</sup> , HSeO <sub>4</sub> <sup>2-</sup> , H <sub>2</sub> SeO <sub>4aq</sub> )
Organic Se	Selenomethionine, selenocysteine

**Table 3.** Selenium (mg/kg) in some common rock types (modified from Fordyce<sup>(15)</sup>)

Igneous rocks	Se	Sedimentary rocks	Se
Ultramafic	0.05	Limestone	0.03–0.08
Mafic	0.05	Sandstone	<0.05
Granitic	0.01–0.05	Shale	0.05–0.06
Volcanic	0.35	Mudstone	0.1–1500
		Phosphates	1–300
		US coal	0.46–10.5

igneous rocks, sandstones and limestones account for 96% of the rock in the upper 16 km of the Earth's crust<sup>(25)</sup>, generally low concentrations of Se are therefore to be expected over much of the Earth's surface.

However, there are exceptions to the generally low levels of Se in some types of sedimentary rocks and deposits. Very high concentrations (>300 mg Se/kg) are reported in some phosphatic rocks, reflecting similarities in the PO<sub>4</sub><sup>3-</sup> and SeO<sub>4</sub><sup>2-</sup> anions<sup>(21–24)</sup>. Coal and other organic-rich deposits tend to have higher levels of Se, with typical ranges from 1 mg/kg to 20 mg/kg, although values of >600 mg/kg are reported for some black shales<sup>(22)</sup>. A summary of the Se content in some common rock types is given in Table 3.

As a chalcophile element (i.e. an element that prefers a sulfide host rather than a silicate one) Se is often found in sulfide mineral deposits in which it substitutes for S in the mineral crystal lattice (e.g. pyrite, chalcopyrite and sphalerite). S and Se have similar ionic radii (Se<sup>2-</sup> 0.184

nm and S<sup>2-</sup> 0.198 nm) and similar electronegativities (Se 2.4 and S 2.5)<sup>(26)</sup>. There are Se minerals such as crookesite (Cu, Tl, Ag<sub>2</sub>Se), clausthalite (PbSe) and berzelianite (Cu<sub>2</sub>Se), but these minerals are rare compared with sulfides. Elemental Se<sup>0</sup> is occasionally reported<sup>(21,24,27)</sup>.

The geographical distribution of Se in an area with diverse geology is likely to be quite variable, reflecting the occurrence of different rock types or sulfide mineral deposits. Higher levels of Se would be expected in environments in which the underlying bedrock consists of the high-Se sedimentary rocks described earlier or because of the occurrence of sulfide mineralisation. This feature is well illustrated by the Wales regional geochemistry map for Se in stream sediments (Fig. 1). This map has been produced by the BGS's Geochemical Baseline Survey of the Environment regional geochemical mapping programme<sup>(28)</sup> and is based on the X-ray fluorescence

**Table 4.** Global selenium fluxes (after Fordyce<sup>(15)</sup> based on data from Haygarth<sup>(13)</sup>)

Cycle	Se flux (t/year)
Anthropogenic	76 000–88 000
Marine	38 250
Terrestrial	15 380
Atmospheric	15 300

spectrometric analysis of approximately 19 000 stream-sediment samples collected at an average density of one sample per 1.5 km<sup>2</sup>. This map of Se shows regional high levels associated with sulfide mineralisation (Parys Mountain, Snowdon and the Harlech Dome) and with rock types that are relatively high in Se (Pembrokeshire and South Wales coalfields and Mercia Mudstone). These levels contrast with the lower concentrations associated with the sandstones and siltstones of mid-Wales. Similar regional geochemical maps for Se in soils and stream sediments are available for central and eastern England<sup>(29)</sup> and Northern Ireland.

An overview of the cycling of Se<sup>(13)</sup> looks at the various compartments in the global cycle to describe the annual Se flux (Table 4). This flux pattern demonstrates two important facts, i.e. that the marine system constitutes the main natural pathway for the cycling of Se but it is anthropogenic activity that is a major source of Se migration. Natural release of Se is estimated to be 4500 t/year compared with the estimated anthropogenic release of 76 000–88 000 t/year, which represents a biospheric enrichment of 17 and indicates the important influence of man in the cycling of Se<sup>(30)</sup>. Common anthropogenic sources of Se in the environment are shown in Table 5. Important sources include the combustion of coal and petroleum fuels, metal extraction processes and the use of phosphate fertilisers and sewage sludge in agriculture.

A combination of natural and anthropogenic controls can be seen in the soil Se from northern Europe (Fig. 2). Although this map from the geochemical atlas of the agricultural soils of Northern Europe<sup>(31)</sup> is based on low-density sampling (one site per 2500 km<sup>2</sup>), it still delineates both natural and anthropogenic features that control the distribution of Se. The higher values in Russia can be related to black shales. On the west coast of Norway high levels of Se are caused by a combination of organic-rich soils and input of Se via sea spray. In Finland high concentrations are associated with agricultural soils (fertiliser supplemented with selenate<sup>(32)</sup>) and in the north very-organic-rich soils (peatland) turned into agricultural fields. The most intriguing feature of this map is that for the part of northern Germany that was sampled there is a clear boundary between low and moderate Se in the top soils. This pattern follows the old East–West Germany border and probably reflects the use of Se-rich fertilisers in the west.

#### *Selenium in soil*

Soil is of fundamental importance in the food chain and is of great importance in determining the Se status of crops and livestock. The world mean value for soils is 0.4

**Table 5.** Common anthropogenic sources of selenium in the environment (after Fordyce<sup>(15)</sup>)

Man-made sources	Comments
Se-based industries	
Metal-processing industries	Important source
Burning of fossil fuels	Important source
Disposal of sewage sludge to land	Typical Se contents 1–17 mg/kg
Agricultural use of pesticides	[K(NH <sub>4</sub> )S] <sub>5</sub> Se
Agricultural use of lime	Typical Se contents 0.08 mg/kg
Agricultural use of manure	Typical Se contents 2.4 mg/kg
Agricultural use of phosphate fertilisers	Typical Se contents 0.08–25 mg/kg

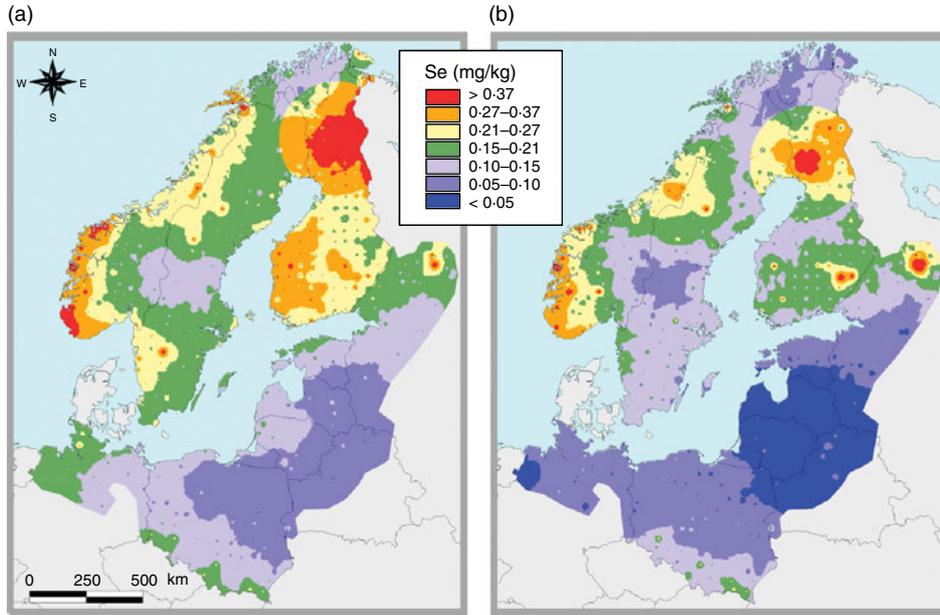
(general range 0.01–2) mg/kg<sup>(15)</sup>. With the exception of instances of anthropogenic modification, in most cases there is a very strong correlation between the concentration of Se in the geological parent material and the soils derived from them. While the geological source of Se is a primary control on soil Se concentration, there are a number of biological and physico-chemical properties that control the Se bioavailability (i.e. the mobility and the uptake by plants and animals) and hence its concentration in foods. These factors include the prevailing pH and redox conditions, the form or speciation of Se, soil texture and mineralogy, organic matter content and the presence of competitive ions<sup>(15)</sup>. Many of these variables and their relationship are illustrated in Fig. 3.

A practical example of the importance of soil Se bioavailability is illustrated by considering two areas of high-Se soils from the USA. In the northern Midwest there are Se toxicity problems in plants and livestock from soils containing 1–10 mg Se/kg because ≤ 60% of the element is readily bioavailable in the semi-arid alkaline environment. In contrast, soils in Hawaii containing as much as 20 mg/kg are not associated with similar toxicity problems because the Se is held in Fe and Al complexes in the humid lateritic soils<sup>(33)</sup>.

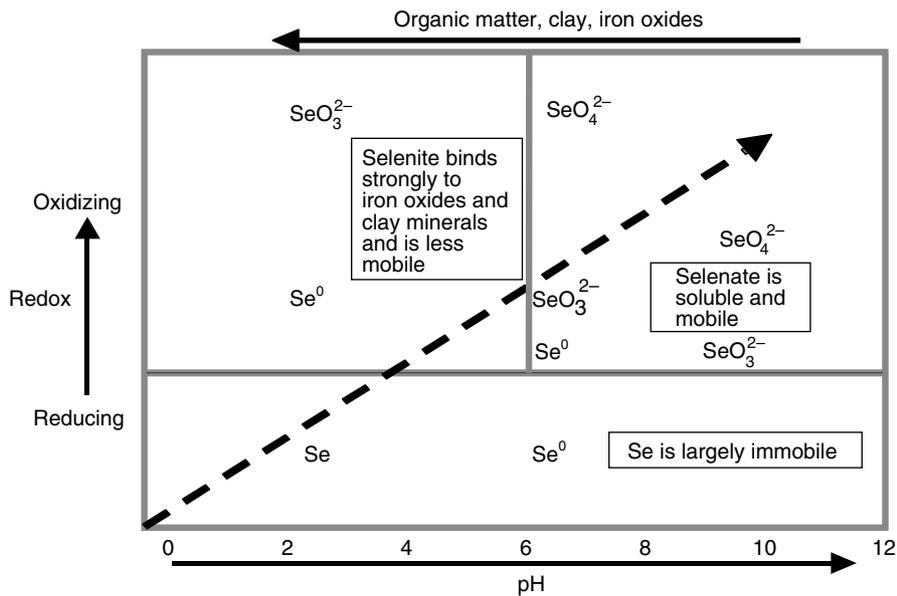
#### **Health impacts of selenium deficiency and toxicity**

The health impacts of Se deficiency and toxicity on both human subjects and livestock are well documented elsewhere (for example, see Rayman<sup>(9)</sup>, Fordyce<sup>(15)</sup>, Reilly<sup>(3)</sup> and Scientific Advisory Committee on Nutrition<sup>(34)</sup>). On a global scale overt Se toxicity in human subjects is far less widespread than deficiency<sup>(15)</sup>. Consequently, the present paper is more focused on deficiency than toxicity.

The recognition of the detrimental effects of too much Se on livestock in the Midwest states of the USA was inevitably followed by studies of Se toxicity in human subjects<sup>(3)</sup>. While initial studies showed elevated urinary Se concentrations in the population but no definite links to clinical symptoms of selenosis, a higher incidence of gastrointestinal problems, poor dental health, diseased nails and skin discolouration, now recognised as symptoms of Se poisoning in human subjects, has been reported<sup>(35)</sup>. Endemic selenosis in China became highlighted in the scientific literature during the 1980s<sup>(36–38)</sup>, although outbreaks of endemic human



**Fig. 2.** Selenium in (a) top (0–25 cm) and (b) bottom (50–75 cm) soils from northern Europe. (After Reimann *et al.*<sup>(31)</sup>.)



**Fig. 3.** Schematic diagram showing the main controls on the chemical speciation and bioavailability of selenium in soils. ---►, Increasing mobility. (After Fordyce<sup>(15)</sup>.)

selenosis occurred in the Enshi District, Hubei Province during the 1960s<sup>(15)</sup>. This condition was found to be associated with high-Se crops grown on soils derived from coal containing >300 mg Se/kg. The main symptoms of Se poisoning in Enshi were observed to be hair and nail loss but disorders of the nervous system, skin, poor dental health, garlic breath and paralysis were also reported and between 1961 and 1964 morbidity rates reached 50% in the worst-affected villages<sup>(15)</sup>. A more modern Se toxicity problem can be related to mineral supplement intake. In the USA in 1984 twelve cases of selenosis were reported when tablets

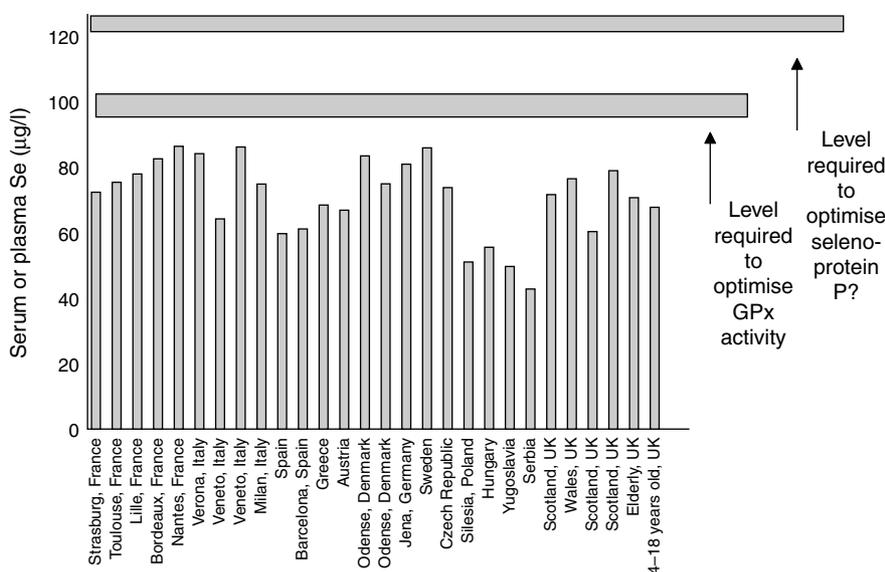
containing 27–31 mg Se (approximately 182 times more than concentrations stated on the label) were taken. Total individual doses estimated to be consumed by the individuals ranged from 27 mg to 2387 mg<sup>(39)</sup>. The low observed adverse effect level for Se is 1540 (SE 653) µg/d<sup>(40)</sup>.

The health impacts of Se deficiency have been discussed in more detail elsewhere<sup>(9,15,41)</sup> and are summarised in Table 6 with conditions being considered under the following headings: mortality; immune function; antiviral effects and HIV; fertility and reproduction; cancer; thyroid effects; CHD.

**Table 6.** Summary of human health conditions that have been related to selenium deficiency

Health condition	Description	References
Overt Se-deficiency diseases	Keshan disease (KD) is an endemic cardiomyopathy (heart disease) characterised by chronic moderate to severe heart enlargement, which can result in death.	Fordyce <sup>(15)</sup> , Li <i>et al.</i> <sup>(44)</sup>
	Exact biological function of Se unclear but KD occurs in Se-deficient areas and responds to Se supplementation. May have viral cause and Coxsackie B virus has been implicated	
Antiviral effects and HIV	Kashin-Beck disease is an endemic osteoarthropathy characterised by chronic disabling degenerative osteoarthritis; the condition is multifactorial with Se deficiency suggested to be one of the factors	Fordyce <sup>(15)</sup>
	Animal studies have shown that the antioxidant selenoenzyme GPx1 inhibits the mutation of viruses to more virulent forms	Beck <i>et al.</i> <sup>(62)</sup>
	Low Se status increases the risk of developing primary liver cancer in hepatitis B/C-positive patients, while Se supplementation of men carrying hepatitis B surface antigen reduces their risk of developing liver cancer	Yu <i>et al.</i> <sup>(63)</sup> , Bjelakovic <i>et al.</i> <sup>(64)</sup>
	In US patients with relatively low Se status (plasma Se <85 µg/l) HIV infection progresses more rapidly to AIDS with higher mortality	Baum <i>et al.</i> <sup>(65)</sup> , Campa <i>et al.</i> <sup>(66)</sup>
Cancer	In a Tanzanian observational study of 949 HIV-positive pregnant women mortality decreases with increase in plasma Se (>85 µg/l) over 5-year follow-up period	Kupka <i>et al.</i> <sup>(67)</sup>
	Inverse relationship between crop and human Se status and cancer incidence in North America	Shamberger & Frost <sup>(68)</sup>
	Evidence for Se as a cancer preventive agent includes that from geographic, animal, prospective and intervention studies. There is evidence that Se reduces the risk of cancers of the prostate, oesophagus and gastric cardia, bladder, liver, lung, thyroid and colo-rectal adenoma (a pre-cancerous lesion)	Summarised in Rayman <sup>(9,45)</sup>
	Supplementation with Se gives a reduction in cancer mortality and incidence of prostate, colo-rectal and lung cancers	Clark <i>et al.</i> <sup>(8)</sup>
Cognitive function	However, Se and vitamin E, alone or in combination, do not prevent prostate cancer in a population with high Se status at baseline	Lippman <i>et al.</i> <sup>(69)</sup>
	During Se depletion the brain receives a priority supply of Se	Rayman <sup>(41)</sup>
	Cognitive function is associated with the magnitude of plasma Se decrease over a 9-year period	Akbaraly <i>et al.</i> <sup>(70)</sup>
CHD	Lower toenail Se is associated with lower cognitive score in rural elderly Chinese	Gao <i>et al.</i> <sup>(71)</sup>
	A meta-analysis of twenty-five observational studies shows that a 50% increase in Se concentrations is associated with a 24% reduction in CHD	Flores-Mateo <i>et al.</i> <sup>(72)</sup>
Fertility and reproduction	The selenoproteins phospholipid GPx4 and sperm nuclei selenoprotein are required for sperm motility and sperm maturation, while selenoprotein-P is required for Se supply to the testes	Summarised in Rayman <sup>(9)</sup>
	Sufficiency of Se intake improves male fertility, reduces the risk of miscarriage and may reduce the risk of pre-eclampsia	Summarised in Rayman <sup>(9)</sup> , Rayman <i>et al.</i> <sup>(73)</sup>
Immune function	Randomised placebo-controlled trials show that Se supplementation of UK adults enhances the cellular response, while supplementation of elderly Belgians restores the age-related decline in immune response	Broome <i>et al.</i> <sup>(74)</sup> , Peretz <i>et al.</i> <sup>(75)</sup>
Mortality	A 12-year follow-up of 13 887 adult participants in the US NHANES III whose serum Se was measured at baseline shows that increasing Se is associated with decreased mortality up to a serum concentration of 130 µg/l	Bleys <i>et al.</i> <sup>(76)</sup>
	A study of 1389 elderly French subjects suggests that low plasma Se concentration at baseline is significantly associated with higher mortality over 9 years	Akbaraly <i>et al.</i> <sup>(77)</sup>
	RCT have found that Se supplementation tends to reduce mortality	Bjelakovic <i>et al.</i> <sup>(78)</sup>
Thyroid effects	The iodothyronine deiodinases that produce the active form of thyroid hormone are selenoenzymes, while the antioxidant selenoenzyme GPx is required for the protection of the thyroid from the H <sub>2</sub> O <sub>2</sub> produced there	Arthur & Beckett <sup>(79)</sup>
	Severe Se deficiency occurs in the endemic goitre belt of north Zaire, which together with iodine deficiency gives rise to myxoedematous cretinism	Vanderpas <i>et al.</i> <sup>(80)</sup>
	An inverse association has been found between Se status and thyroid volume, thyroid tissue damage and goitre in French women	Derumeaux <i>et al.</i> <sup>(81)</sup>
	In RCT in patients with thyroid peroxidase antibodies or autoimmune thyroiditis Se supplementation decreases inflammation and thyroid antibody concentrations and prevents postpartum hypothyroidism	Summarised in Rayman <sup>(9)</sup>

GPx, glutathione peroxidase; NHANES III, Third National Health and Nutrition Examination Survey; RCT, randomised controlled trials.



**Fig. 4.** Concentrations of selenium in human serum and plasma in Europe. GPx, glutathione peroxidase. (After Rayman<sup>(41)</sup>.)

Se has a lower reference nutrient intake value of 40 µg/d for males and females, and a reference nutrient intake of 60 µg/d for females and 75 µg/d for males<sup>(42)</sup>. Optimal intakes must consider the species of Se ingested, the medical condition being addressed, the overall nutritional adequacy of the group or population, the extent to which genomic differences between individuals or populations may be relevant, other risk or lifestyle factors that may be present and, most importantly, the background Se intake in that population (for discussion, see Rayman<sup>(9)</sup>).

In the body Se is used as part of a group of molecules known as selenoproteins that contain the amino acid seleno-cysteine. These selenoproteins have a variety of functions including: glutathione peroxidase, antioxidant defence; thio-redoxin reductase, cell redox control; selenoprotein SEPS1, anti-inflammatory; selenoprotein P, Se transport in the plasma<sup>(43)</sup>.

Keshan disease (KD) is a medical condition in human subjects that is associated with Se deficiency and the subject of a case study highlighted later in the present paper. It is an endemic cardiomyopathy (heart disease) that derives its name from substantial occurrences in Keshan County, north-east China, with annual prevalence exceeding forty cases per 100 000 of the population and 1400–3000 deaths per year<sup>(38)</sup>. Affected populations are characterised by very low Se status as indicated by hair Se contents. Like many of the conditions associated with Se deficiency there are believed to be other contributory factors to KD. More recent studies (for example, see Li *et al.*<sup>(44)</sup>) have demonstrated a high prevalence of the Coxsackie B virus in patients with KD, which is now thought to be a cofactor in the disease.

#### Selenium status in human subjects is linked to the environment

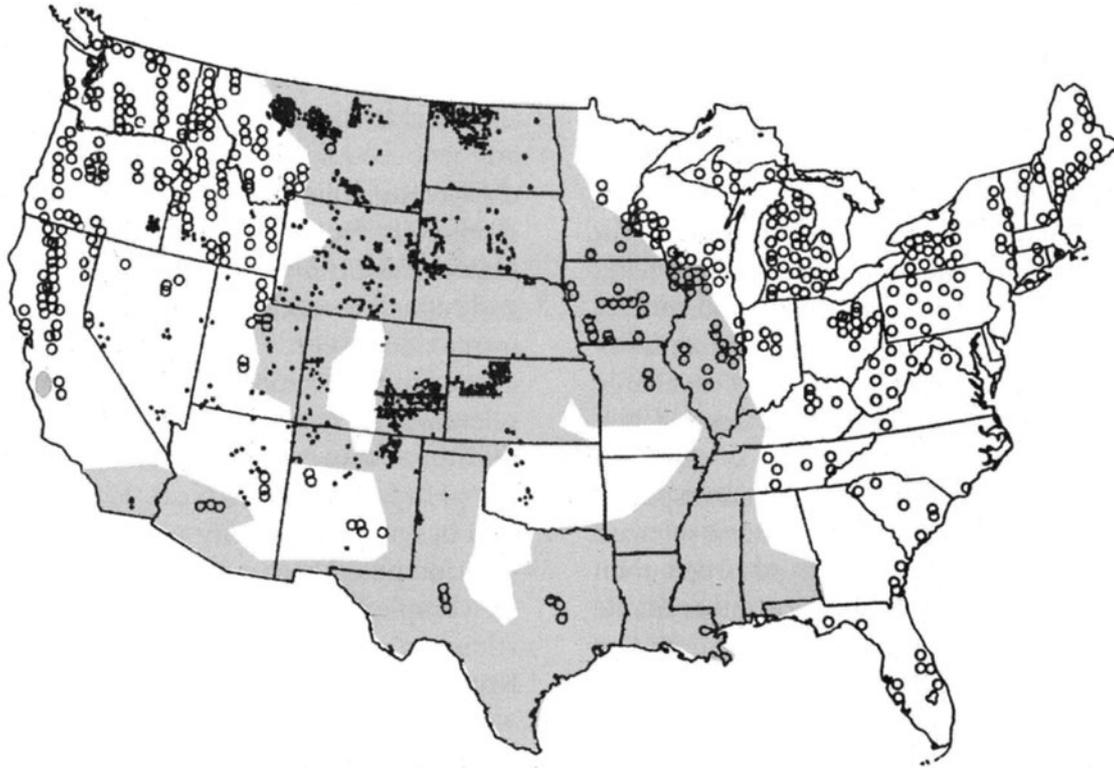
Se status in human subjects can be assessed by determining Se levels in blood (whole blood, serum or plasma), hair,

nails and urine<sup>(3)</sup>. The geochemistry of Se described earlier provides a guide to the relative amounts of Se that may be expected in a particular geological setting and studies of Se in the soil, drainage sediments, water and crops give an indication of environmental Se status.

It has been noted that there is a marked variation in Se intake and status (as measured in blood, plasma or serum, toenails or hair) from one part of the world to another and even between different parts of the same country<sup>(41,45)</sup>. Fig. 4 shows serum or plasma Se levels from a compilation of European studies and puts these data in the context of the optimal levels required for glutathione peroxidase and selenoprotein P activity. These data for Europe, especially when put into the context of US serum Se levels of 125–137 µg/l (as measured in recent US National Health and Nutrition Examination Surveys<sup>(46,47)</sup>), demonstrate that European populations are generally of low Se status. Hair analysis has been used in several studies of Se status in China<sup>(48)</sup> and is also the method that was used by the BGS's Se case studies carried out in China in the 1990s<sup>(16,49,50)</sup>. Whilst the methodology for hair sampling is not generally standardised and the hair can be contaminated from external sources (e.g. Se-containing shampoos), it is a technique that can be easily carried out by non-medical personnel.

The importance of understanding Se speciation in relation to its distribution and behaviour in soils has been discussed earlier. An understanding of food-chain Se and health equally needs knowledge of more than only total Se concentrations. Health effects, both beneficial and toxic, thought to be associated with specific Se species are described elsewhere<sup>(51)</sup>.

Baseline geochemical maps (e.g. Fig. 1) give an immediate impression of whether there is high or low Se in the environment, although it is only in recent years that such baseline maps have been produced. Statistical analysis of such large data sets when they become available will enable good comparisons between the environmental



**Fig. 5.** Indicators of environmental selenium status for the USA. (■), Selenium-rich environments; (●), plant selenium >50 mg/kg; (○), white muscle disease incidence. (From Fordyce<sup>(15)</sup>, adapted from Muth & Allaway<sup>(52)</sup>.)

Se status of different countries or regions of the world. Fig. 5 demonstrates that where a good dependence on the local environment can be shown, other environmental indicators such as plant Se concentrations and Se-deficiency diseases in livestock (e.g. white muscle disease) can be used to indicate environmental Se status<sup>(52)</sup>.

#### Case study: Zhangjiakou District of China

In the late 1990s the BGS carried out a project on 'prediction and remediation of human Se imbalances' in China supported by the UK Department for International Development. The objective of the project was to develop a methodology for delineating where Se deficiency or toxicity posed a health risk. The environmental geochemical controls on the distribution of Se-responsive diseases were also evaluated. The case study carried out in the KD belt in the Zhangjiakou District<sup>(16)</sup> serves as a good example of how the environmental and human Se status can be determined and compared.

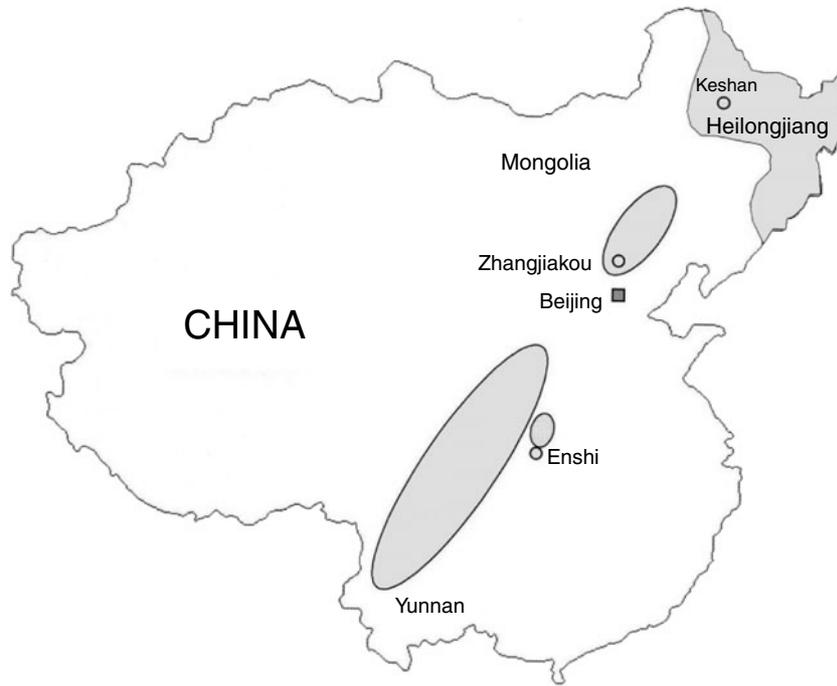
On a regional scale the area investigated is part of the KD belt shown as being a Se-deficient ecological landscape<sup>(38)</sup> (Fig. 6). However, within this belt some villages were found to be more susceptible to KD than others. The case study in Zhangjiakou District was designed to look at villages on a local scale in order to determine which factors could account for high incidences of KD in some villages whilst other villages in the same county had moderate or no incidence of the disease. The study was constrained by budget to a 10 d period of fieldwork and

was timed to coincide with the harvest so that the wheat and the soil on which it was grown could be sampled simultaneously.

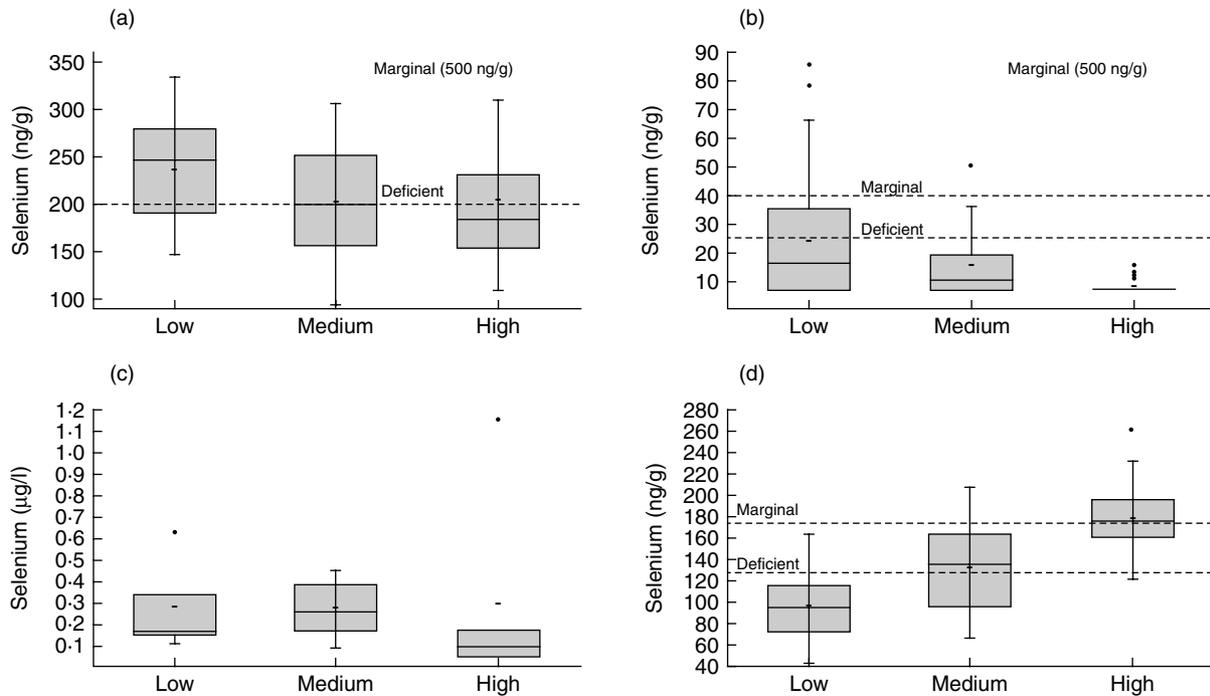
The investigation has been described in more detail<sup>(16)</sup> and the following is a summary account. The project was a collaboration with the Chinese Institute of Rock and Mineral Analysis and depended on the excellent medical records that documented the health of every villager in the target communes. The sampling strategy targeted fifteen villages within the Se-deficiency belt: five with no incidence of KD; five with moderate incidence (>0–3%); five with high incidence (>3%). From each village five samples of soil and grain and one sample of the village drinking water were collected to represent the Se status of the local environment and five human hair samples to represent the human Se status.

Much of the area was quite mountainous, making access difficult. Villages (populations of 200–400) were quite isolated and connected by dirt tracks that were impassable during bad weather. This isolation of villages and the near subsistence level of existence made the region ideal for investigating how local environmental factors were influencing the rates of incidence of KD.

Se was determined using hydride-generation atomic fluorescence spectroscopy and a summary of the Se results for the four sample media is shown in Fig. 7. It is clear that both the human Se status (as indicated by hair) and the environmental Se status (as indicated by water, grain and soil) are Se deficient. The grain values are less than half those reported for UK wheat and soil values are one-quarter to half the UK average. The thresholds for



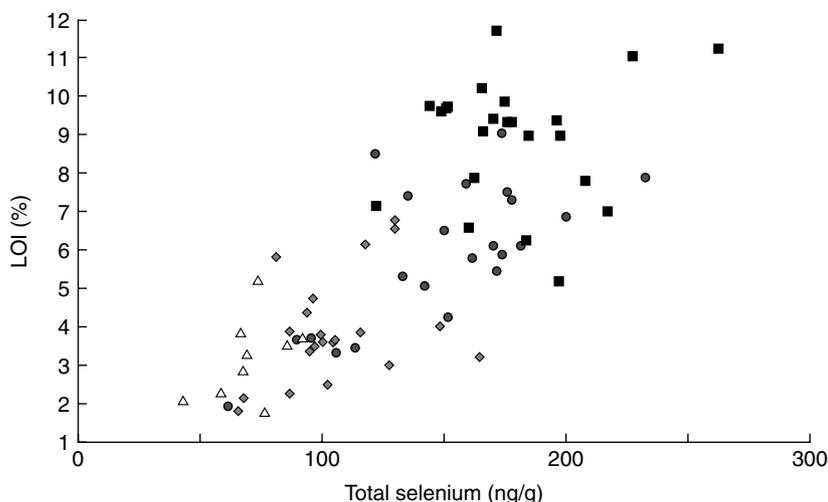
**Fig. 6.** Map showing the location of the Zhangjiakou case study area. (□), Keshan disease belt. (Adapted from Tan<sup>(38)</sup> with permission.).



**Fig. 7.** Box and whisker plots showing the selenium content of the four sample types (human hair (a), grain (b), drinking water (c) and soil (d)) classified by incidence of Keshan disease in the local population in Zhangjiakou District, China. Plots were created using UNISTAT<sup>®</sup> (v4.5) statistical software (Unistat Ltd, London, UK). Medians are represented by horizontal bars within the box and upper and lower quartiles  $\pm 1.5 \times$  quartile range are represented by the whiskers. (–), Arithmetic mean; (·), outlying values. For a discussion of marginal and deficient thresholds, see text. (After Johnson *et al.*<sup>(16)</sup>.)

environmental deficiency shown in Fig. 7 are based on data from the *The Atlas of Endemic Diseases and their Environments in the People’s Republic of China*<sup>(38)</sup> and are

discussed in more detail elsewhere<sup>(15)</sup>. For the hair, drinking water and grain results the trend is as would be expected, with the villages showing a high incidence of



**Fig. 8.** A plot of loss on ignition (representing soil organic matter content) v. total selenium in soils from the Zhangjiakou District, China classified by soil colour. (■), Black; (●), brown-black; (◆), yellow-black; (△), yellow. (After Johnson *et al.*<sup>(16)</sup>.)

KD having the least Se. However, soils show the opposite trend; whilst levels are still very low, the highest concentrations of soil Se are found in fields surrounding villages with the highest incidences of KD.

An explanation for this paradox can be seen by looking at some of the other variables determined for the soil samples. The overall total soil Se content is low and with water-extractable Se representing generally <1% of the total the determination of the very low concentrations of water-extractable Se was found to be very difficult. However, the higher percentage of water-extractable Se is present in the samples from villages with no incidences of KD and the majority of samples from villages with high incidence of KD have extractable Se concentrations below detection; thus indicating that the problem in villages with a high incidence of KD is that the little amount of Se that is available in this environment is not being released from the soils. Determination of a full range of chemical elements and other variables in the soils and statistical analysis of the data shows good correlation between total Se and the organic matter content of the soil (as estimated by loss on ignition; Fig. 8). This plot is very revealing, particularly if the soil sites are classified by their colour as an indication of soil type. Clearly, the black, organic-rich soils have the least-mobile Se content. The conclusion from the Zhangjiakou study is that in an already-Se-deficient environment soil characteristics will have a very marked localised impact on Se availability to the food chain and it is very important to take into account the bioavailability of the Se in the environment.

#### Health impact of environmental selenium deficiency can be seen where food is sourced locally

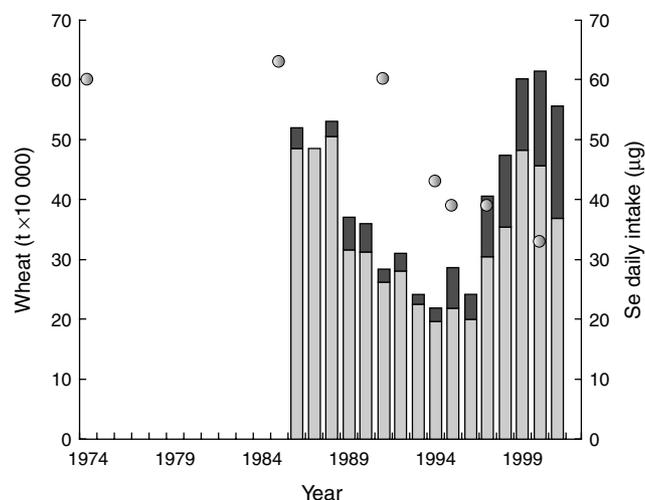
The BGS case studies in China have demonstrated that the health impacts of Se deficiency in human subjects can be related to the level of Se in the environment if the local inhabitants are dependent on their immediate surroundings

for sustenance. In urbanised and developed regions of the world in which populations are less dependent on their immediate environment for foodstuffs and drinking water, establishing a link is more difficult. However, maps such as Fig. 1 are invaluable in understanding the Se concentrations in crops and livestock and can be used to predict which areas will have an imbalance in Se concentrations in agricultural products. An effective application of Se through fertilisers must be demonstrably safe to the environment and monitored appropriately. In the UK the quality and quantity of baseline geochemical data will enable such monitoring to be undertaken with confidence<sup>(53)</sup>.

#### The recent decline in selenium status in the UK

Data on human Se intake (for example, see data from the UK Total Diet Study<sup>(34)</sup> and from Rayman<sup>(45)</sup>) clearly demonstrate that in the UK intake has been falling and is now demonstrably less than the range of Se intakes believed to be required for the optimal activity or concentration of some essential plasma selenoproteins (see UK data in Fig. 4). The UK Total Diet Study shows a drop in Se intake from 60 µg/d in the 1980s to approximately half that value by 2000<sup>(34)</sup> (Fig. 9), leaving it well below reference nutrient intake values (60 µg/d and 75 µg/d for adult females and males respectively<sup>(42)</sup>). Whilst geological controls can account for the generally low concentrations in UK crops relative to North America, it is anthropogenic activities that are thought to have led to a decline in the Se status of the UK population and most of Europe. The following summarises the possible causes of declining Se status:

1. changes in bread-making technology allowing the use of low-protein low-Se EU and UK wheat rather than high-protein high-Se wheat from North America<sup>(54)</sup>;
2. changing dietary patterns; in northern Europe meat and poultry are the main sources of dietary intake of Se. A decline in meat eating, particularly good sources



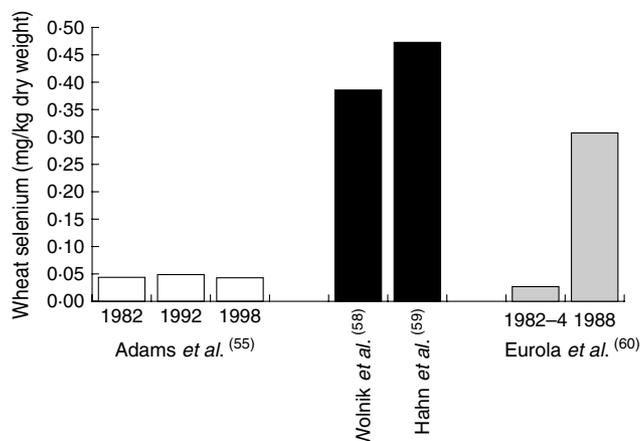
**Fig. 9.** Plot of UK wheat imports from North America (■, USA; □, Canada) in the context of the UK daily selenium intake (○). Daily selenium intake from the UK Total Diet Study (see Table 6 from Scientific Advisory Committee on Nutrition<sup>(34)</sup>) and wheat import data (starting in 1986) from FAOSTAT (Food and Agriculture Organization<sup>(82)</sup>; detailed trade matrix).

of Se such as liver and kidney, will result in a decline in dietary Se intake unless replaced by foodstuffs of equally-high Se content. The Scientific Advisory Committee on Nutrition<sup>(34)</sup> reports that the main source of Se in the UK diet are breads, cereals, fish, poultry and meat and that rich dietary sources of Se include brazil nuts (*Bertholletia excelsa*), fish and offal;

- reduced atmospheric deposition from fossil-fuel burning has reduced Se input into the surface environment. Coal can potentially be a very rich source of Se<sup>(15)</sup>;
- increased use of S fertilisers to overcome S deficiency in arable crops has meant that there is increased competition between S and Se in crop uptake<sup>(55)</sup>. S inputs from fertilisers and atmospheric deposition have an important influence on the Se status of wheat grain<sup>(56)</sup>.

#### Relationship between selenium status and environmental selenium from crops

The contrast between the Se status of North American and UK wheat is another good example of how environmental Se status impacts on crops. BGS data for >22 000 topsoils from central and eastern England show a median value of 0.3 mg Se/kg (British Geological Survey, unpublished results). This value can be contrasted with that for soils from the Se-deficiency belt of China (Fig. 7) that have median values of 0.13 mg Se/kg and those of soils developed on the cretaceous shale of South Dakota, Montana, Wyoming, Nebraska, Kansas, Utah, Colorado and New Mexico in the USA that have Se contents ranging from 2 mg/kg to 10 mg/kg<sup>(57)</sup> (see Fig. 5). The Se content of wheat grain from these areas reflects the soil concentrations, with 0.025, 0.016 and 0.37–0.46 mg/kg for wheat grain from the UK<sup>(55)</sup>, Zhangjiakou (China)<sup>(16)</sup> and



**Fig. 10.** A comparison of UK (□), US (■) and Finnish (□) wheat selenium concentrations. Data for Finnish wheat grain<sup>(60)</sup> represent values obtained before and after supplementation of fertilisers with sodium selenate<sup>(32)</sup>.

USA<sup>(58,59)</sup> respectively. There is a >10-fold difference in Se concentrations between UK and USA wheat, so it is easy to comprehend that a decline in the use of North American wheat will result in a decline in Se in the UK diet. This contrasting content of Se in wheat grain from the UK and USA is illustrated in Fig. 10. Data for wheat grain<sup>(60)</sup> before and after Finnish supplementation of fertilisers with sodium selenate<sup>(32)</sup> is also illustrated in Fig. 10 to demonstrate the success of this programme in raising the wheat grain Se content. As a consequence, the Se intake in Finland has grown from about 30 µg/d to 100 µg/d<sup>(61)</sup>.

#### North American wheat is now imported for more than UK bread making

When the UK import of wheat from North America is shown together with the UK daily Se intake over a period of several decades (Fig. 9) it can be seen that in the 1990s the daily intake levels of Se did indeed drop with the declining imports of North American wheat. However, although wheat imports at the end of the 1990s are higher than pre-1990 levels, there is no marked increase in the UK daily Se intake, as shown by the daily Se intake measured in 2000. This outcome would suggest that current Se intake levels no longer simply reflect North American wheat imports; the imported wheat must now be being put to some other use.

#### Conclusions

It has been demonstrated that Se intake and status can be closely related to the concentration, solid-phase distribution and speciation of Se in the local environment, which is largely determined by the prevailing geochemical and soil characteristics. Knowledge of such factors can suggest health risks that might be relevant to a country or region by predicting which locations might be characterised by Se deficiency or toxicity. However, this direct relationship is

more difficult to demonstrate in modern societies that do not rely on the local environment for sustenance. Geochemical baseline data have a role to play in implementing effective fertiliser supplementation programmes and monitoring the consequences. Improved analytical methods enable high-resolution geochemical baselines for Se in a variety of environmental media to be produced. More work needs to be done to integrate the spatially-referenced Se databases that exist for geochemical materials (e.g. soil and drainage sediments) and crops (e.g. wheat). Collaboration between geologists, plant scientists, epidemiologists and nutritionists has much to contribute in the study of factors affecting human health.

### Acknowledgements

C. C. J. and F. M. F. acknowledge the contributions made to the BGS Se projects by Don Appleton (Project Manager) and the excellent cooperation from Chinese colleagues at the Institute of Rock and Mineral Analysis who made the Chinese case studies possible and initiated their interests in Se geochemistry. This paper is published with permission of the Director of the British Geological Survey (Natural Environment Research Council). The authors declare no conflict of interest. This publication received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. C. C. J. presented the lecture and led the preparation of the manuscript. The paper is based on the international expertise and substantial contributions made by F. M. F. in the field of Se geochemistry and many of the tables and figures are based on her work. Contributions on medical and health impact information have been provided by M. P. R., notably Table 6 and data on human Se status.

### References

- Smith MI, Franke KW & Westfall BB (1936) The selenium problem in relation to public health. *Public Health Rep* **51**, 1496–1505.
- Moxon AL (1937) *Alkali Disease or Selenium Poisoning*. South Dakota Agricultural Experiment Station Bulletin no. 311. Brookings, SD: Agricultural Experiment Station, South Dakota State College of Agriculture and Mechanical Arts.
- Reilly C (2006) *Selenium in Food and Health*, 2nd ed. New York: Springer.
- Rosenfeld I & Beath OA (1964) *Selenium Geobotany, Biochemistry, Toxicity and Nutrition*, p. 7. New York: Academic Press.
- Shao S & Zheng B (2008) The biogeochemistry of selenium in Sunan grassland, Gansu, Northwest China, casts doubt on the belief that Marco Polo reported selenosis for the first time in history. *Environ Geochem Health* **30**, 307–314.
- Scharz K & Foltz CM (1957) Selenium as an integral part of Factor 3 against dietary necrotic liver degeneration. *J Am Chem Soc* **79**, 3292–3293.
- Rotruck JT, Pope AL, Ganther HE *et al.* (1972) Prevention of oxidative damage to rat erythrocytes by dietary selenium. *J Nutr* **102**, 689–696.
- Clarke LC, Combs GF Jr, Turnbull BW *et al.* (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomised controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* **276**, 1957–1963.
- Rayman MP (2008) Food-chain selenium and health: emphasis on intake. *Br J Nutr* **100**, 254–268.
- Shriver DF & Atkins PW (1999) *Inorganic Chemistry*, 3rd ed. Oxford: Oxford University Press.
- Thornton I, Kinniburgh DG, Pullen G *et al.* (1983) Geochemical aspects of selenium in British soils and implications to animal health. In *Trace Substances in Environmental Health* 17, pp. 391–398 [DD Hemphill, editor]. Columbia, MO: University of Missouri Press.
- McNeal JM & Balistrieri LS (1989) Geochemistry and occurrence of selenium: An overview. In *Selenium in Agriculture and the Environment*. Soil Science Society of America Special Publication no. 23, pp. 1–14 [LW Jacob, editor]. Madison, WI: American Society of Agronomy and Soil Science Society of America.
- Haygarth PM (1994) Global importance and cycling of selenium. In *Selenium in the Environment*, pp. 1–28 [WT Frankenberger and S Benson, editors]. New York: Marcel-Dekker.
- Plant JA, Kinniburgh DG, Smedley PL *et al.* (2003) Arsenic and selenium. In *Treatise on Geochemistry*. vol. 9, *Environmental Geochemistry*, pp. 17–66 [BS Lollar, HD Holland and KK Turekian, editors]. London: Elsevier.
- Fordyce FM (2005) Selenium deficiency and toxicity in the environment. In *Essentials of Medical Geology*, pp. 373–415 [O Selinus, B Alloway, JA Centeno, RB Finkelman, R Fuge, U Lindh and P Smedley, editors]. London: Elsevier.
- Johnson CC, Ge X, Green KA *et al.* (2000) Selenium distribution in the local environment of selected villages of the Keshan Disease belt, Zhangjiakou District, Hebei Province, People's Republic of China. *Appl Geochem* **15**, 385–401.
- British Geological Survey (2000) *Regional Geochemistry of Wales and Part of West-Central England: Stream Sediment and Soil*. Nottingham: British Geological Survey.
- Mikkelsen RL, Page AL & Bingham FT (1989) Factors affecting selenium accumulation by agricultural crops. In *Selenium in Agriculture and the Environment*. Soil Science Society of America Special Publication no. 23, pp. 65–94 [LW Jacob, editor]. Madison, WI: American Society of Agronomy and Soil Science Society of America.
- Taylor SR & McLennan SM (1985) *The Continental Crust: Its Composition and Evolution*. Oxford: Blackwell.
- Fergusson JE (1990) *The Heavy Elements: Chemistry, Environmental Impact and Health Effects*. London: Pergamon Press.
- Flemming GA (1980) Essential micronutrients II: iodine and selenium. In *Applied Soil Trace Elements*, pp. 199–234 [BE Davis, editor]. New York: John Wiley & Sons.
- Jacobs LW (editor) (1989) *Selenium in Agriculture and the Environment*. Soil Science Society of America Special Publication no. 23. Madison, WI: American Society of Agronomy and Soil Science Society of America.
- Nriagu JO (1989) *Occurrence and Distribution of Selenium*. Boca Raton, FL: CRC Press.
- Neal RH (1995) Selenium. In *Heavy Metals in Soils*, pp. 260–283 [BJ Alloway, editor]. London: Blackie Academic and Professional.
- Clarke FW & Washington HS (1924) *The Composition of the Earth's Crust*. US Geological Survey Professional Paper no. 127. Washington, DC: US Government Printing Office.
- Pauling L (1970) *General Geochemistry*, 3rd ed. San Francisco, CA: WH Freeman & Co.
- Tokunaga T, Pickering I & Brown G (1996) Selenium transformations in ponded sediments. *Soil Sci Soc Am J* **60**, 781–790.

28. Johnson CC, Breward N, Ander EL *et al.* (2005) G-BASE: baseline geochemical mapping of Great Britain and Northern Ireland. *Geochem Explor Environ Anal* **5**, 347–357.
29. Ander EL, Johnson CC, Fordyce FM *et al.* (2008) Iodine and selenium in soils from East Anglia, UK. *Geophys Res Abstr* **10**, EGU2008-A-09267; <http://www.cosis.net/abstracts/EGU2008/09267/EGU2008-A-09267.pdf> (accessed October 2009).
30. Allan RJ & Nriagu JO (editors) (1993) In *Heavy Metals in the Environment IX*, vol. 1. Edinburgh: CEP Consultants Ltd.
31. Reimann C, Siewers U, Tarvainen T *et al.* (editors) (2003) *Agricultural Soils in Northern Europe: A Geochemical Atlas*, special ed. series D–Geol Jahrb. Stuttgart, Germany: E. Schweizerbart'sche Verlagsbuchhandlung.
32. Aro A, Alfthan G & Varo P (1995) Effects of supplementation of fertilisers on human selenium status in Finland. *Analyst* **120**, 841–843.
33. Oldfield JE (1999) *Selenium World Atlas*. Grimbergen, Belgium: Selenium–Tellurium Development Association.
34. Scientific Advisory Committee on Nutrition (2007) Paper for approval: selenium and health paper. SACN/07/24. [http://www.sacn.gov.uk/pdfs/sacn\\_07\\_24.pdf](http://www.sacn.gov.uk/pdfs/sacn_07_24.pdf) (accessed July 2009).
35. Smith MI & Westfall BB (1937) Further field studies on the selenium problem in relation to public health. *Public Health Rep* **52**, 1375–1384.
36. Yang G, Wang S, Zhou R *et al.* (1983) Endemic selenium intoxication of humans in China. *Am J Clin Nutr* **37**, 872–881.
37. Yang, G, Yin S, Zhou R *et al.* (1989) Studies of safe and maximal daily dietary selenium intake in seleniferous areas in China. Part 2. *J Trace Elem Electrolytes Health Dis* **3**, 123–129.
38. Tan J (editor) (1989) *The Atlas of Endemic Diseases and their Environments in the People's Republic of China*. Beijing, China: Science Press.
39. World Health Organization (1987) Environmental health criteria 58 – Selenium. <http://www.inchem.org/documents/ehc/ehc/ehc58.htm> (accessed August 2009).
40. Whanger P, Vendeland S, Park YC *et al.* (1996) Metabolism of subtoxic levels of selenium in animals and humans. *Ann Clin Lab Sci* **26**, 99–113.
41. Rayman MP (2000) The importance of selenium to human health. *Lancet* **356**, 233–241.
42. Department of Health (1991) *Dietary Reference Values for Food Energy & Nutrients for the UK. Report on Health and Social Subjects* no. 41. London: H. M. Stationery Office.
43. Papp LV, Lu J, Holmgren A *et al.* (2007) From selenium to selenoproteins: synthesis, identity, and their role in human health. *Antioxid Redox Signal* **7**, 775–806.
44. Li Y, Peng T, Yang Y *et al.* (2000) High prevalence of enteroviral genomic sequences in myocardium from cases of endemic cardiomyopathy (Keshan Disease) in China. *Heart* **83**, 696–701.
45. Rayman MP (2005) Se in cancer prevention: a review of the evidence and mechanism of action. *Proc Nutr Soc* **64**, 527–542.
46. Niskar AS, Paschal DC, Kieszak SM *et al.* (2003) Serum selenium levels in the US population: Third National Health and Nutrition Examination Survey, 1988–1994. *Biol Trace Elem Res* **91**, 1–10.
47. Bleys J, Navas-Acien A, Laclaustra M *et al.* (2003) Serum selenium and peripheral arterial disease: results from the national health and nutrition examination survey, 2003–2004. *Am J Epidemiol* **169**, 996–1003.
48. Chen X, Yang G, Chen JS *et al.* (1980) Studies on the relations of selenium to Keshan Disease. *Biol Trace Elem Res* **2**, 91–104.
49. Fordyce FM, Zhang G, Green K *et al.* (2000) Soil, grain and water chemistry and human selenium imbalances in Enshi District, Hubei Province, China. *Appl Geochem* **15**, 117–132.
50. Appleton JD, Zhang Q, Green KA *et al.* (2006) Selenium in soil, grain, human hair and drinking water in relation to esophageal cancer in the Cixian area, Hebei Province, People's Republic of China. *Appl Geochem* **21**, 684–700.
51. Rayman MP (2008) Food-chain selenium and health: spotlight on speciation. *Br J Nutr* **100**, 238–253.
52. Muth OH & Allaway WH (1963) The relationship of White Muscle Disease to the distribution of naturally occurring selenium. *J Am Vet Med Assoc* **142**, 1379–1384.
53. Broadley MR, White PJ, Bryson RJ *et al.* (2006) Biofortification of UK food crops with selenium. *Proc Nutr Soc* **65**, 169–181.
54. Whitley A (2006) *Bread Matters: The State of Modern Bread and a Definitive Guide to Baking Your Own*. London: Fourth Estate Ltd.
55. Adams LA, Lombi E, Zhao F-J *et al.* (2002) Evidence of low selenium concentrations in UK bread-making wheat grain. *J Sci Food Agric* **82**, 1160–1165.
56. Fan M-S, Zhao F-J, Poulton PR *et al.* (2008) Historical changes in the concentrations of selenium in soil and wheat grain from the Broadbalk experiment over the last 160 years. *Sci Total Environ* **389**, 532–538.
57. Jackson ML (1964) *Chemistry of the Soil*, 2nd ed. [FE Bear, editor]. New York: Reinhold.
58. Wolnik KA, Fricke FL, Capar GL *et al.* (1983) Elements in major raw agricultural crops in the United States. 2. Other elements in lettuce, peanuts, potatoes, soybeans, sweet corn, and wheat. *J Agric Food Chem* **31**, 1244–1249.
59. Hahn MH, Kuennen RW, Caruso JA *et al.* (1981) Determination of trace amounts of selenium in corn, lettuce, potatoes, soybeans, and wheat by hydride generation/condensation and flame atomic absorption spectrometry. *J Agric Food Chem* **29**, 792–796.
60. Euroala M, Ekholm P, Ylinen M *et al.* (1990) Effects of selenium fertilisation on the selenium content of cereal grains, flour, and bread produced in Finland. *Cereal Chem* **67**, 334–337.
61. Paivi E, Maija Y, Pekka K *et al.* (1995) Selenium concentration of Finnish food – effects of reducing the amount of selenate in fertilisers. *Agric Sci Finl* **4**, 377–384.
62. Beck MA, Esworthy RS, Ho Y-S *et al.* (1998) Glutathione peroxidase protects mice from viral-induced myocarditis. *FASEB J* **12**, 1143–1149.
63. Yu MW, Horng IS, Hsu KH *et al.* (1999) Plasma selenium levels and the risk of hepatocellular carcinoma among men with chronic hepatitis virus infection. *Am J Epidemiol* **150**, 367–374.
64. Bjelakovic G, Nikolova D, Simonetti RG *et al.* (2004) Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* **364**, 1219–1228.
65. Baum MK, Shor-Posner G, Lai S *et al.* (1997) High risk of HIV-related mortality is associated with selenium deficiency. *J Acquir Immune Defic Syndr* **15**, 370–374.
66. Campa A, Shor-Posner G, Indacochea F *et al.* (1999) Mortality risk in selenium-deficient HIV-positive children. *J Acquir Immune Defic Syndr Hum Retrovirol* **20**, 508–513.
67. Kupka R, Msamanga GI & Spiegelman D (2004) Se status is associated with accelerated HIV disease progression among HIV-infected pregnant women in Tanzania. *J Nutr* **134**, 2556–2560.

68. Shamberger RJ & Frost DV (1969). Possible protective effect of Se against human cancer. *Can Med Assoc J* **100**, 682.
69. Lippman SM, Klein EA, Goodman PJ *et al.* (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: The selenium and vitamin E Cancer Prevention Trial (SELECT). *JAMA* **301**, 39–511.
70. Akbaraly NT, Hininger-Favier I, Carriere I *et al.* (2007) Plasma selenium over time and cognitive decline in the elderly. *Epidemiology* **18**, 52–58.
71. Gao S, Jin Y, Hall KS *et al.* (2007) Selenium level and cognitive function in rural elderly Chinese. *Am J Epidemiol* **165**, 955–965.
72. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R *et al.* (2006) Selenium and coronary heart disease: a meta-analysis. *Am J Clin Nutr* **84**, 762–773.
73. Rayman MP, Bode P & Redman CW (2003) Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom. *Am J Obstet Gynecol* **189**, 1343–1349.
74. Broome CS, McArdle F, Kyle JA *et al.* (2004). An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. *Am J Clin Nutr* **80**, 154–162.
75. Peretz A, Neve J, Desmedt J *et al.* (1991) Lymphocyte response is enhanced by supplementation of elderly subjects with selenium-enriched yeast. *Am J Clin Nutr* **53**, 1323–1328.
76. Bleyts J, Navas-Acien A & Guallar E (2008) Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch Intern Med* **168**, 404–410.
77. Akbaraly NT, Arnaud J, Hininger-Favier I *et al.* (2005) Selenium and mortality in the elderly: results from the EVA study. *Clin Chem* **51**, 2117–2123.
78. Bjelakovic G, Nikolova D, Gluud LL *et al.* (2007) Mortality in randomised trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* **297**, 842–857.
79. Arthur JR & Beckett GJ (1999) Thyroid function. *Br Med Bull* **55**, 658–668.
80. Vanderpas JB, Contempré B, Duale NL *et al.* (1990) Iodine and selenium deficiency associated with cretinism in Northern Zaire. *Am J Clin Nutr* **52**, 1087–1093.
81. Derumeaux H, Valeix P, Castetbon K *et al.* (2003) Association of selenium with thyroid volume and echostructure in 35- to 60-year-old French adults. *Eur J Endocrinol* **148**, 309–315.
82. Food and Agriculture Organization (2009) FAOSTAT. Detailed trade matrix web access to data for UK import of USA and Canadian wheat. <http://faostat.fao.org/site/537/default.aspx> (accessed August 2009).