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**MERCURY POLLUTION:** METHYLMERCURY EXPOSURE, HEALTH EFFECTS, HUMANS, WILD BIRDS, MAMMALS, FISH • MERCURY DEPOSITION, SOURCES • CONTAMINATED FISHERIES • SOCIO-ECONOMIC CONSEQUENCES

**MEDICAL GEOLOGY:** EPIDEMIOLOGICAL TRANSITION • IODINE DEFICIENCY • MINEROGENIC DUST • GEOGENIC ARSENIC • BLACKFOOT DISEASE • RADON • SELENIUM DEFICIENCY, GEOCHEMISTRY • COAL, TOXIC ORGANIC SUBSTANCES, HEALTH EFFECTS • METAL BIOLOGY • MEDICAL GEOLOGY, OPPORTUNITY

# Preface to Medical Geology Papers

**The following articles in this issue of *Ambio* deal with the subject of Medical Geology. Specific topics are referred to by author's name within parentheses.**

“Medical Geology” is the science dealing with the relationship between natural geological factors and health in man and animals, and understanding the influence of such relationships on the geographical distribution of health problems. Medical Geology is a broad and complicated subject, which requires interdisciplinary contributions if the problems are to be understood, mitigated and/or resolved (Selinus, Weinstein).

Our environment is the entire web of geological and biological interactions that characterize the relationship between life and planet Earth, and as such has an important bearing on health and well-being. Many of us take for granted that nature will provide a benign environment. It may even be that we do not think of our natural environment as important for our health. However, some naturally occurring elements are necessary for health and well-being while others may have detrimental effects. Geological processes along with human activities have redistributed metals from sites where they are fairly harmless to new sites where they have negative effects on humans and animals (Lindh, Munthe). Essential and toxic elements in bedrock or soils are ingested via food and water, and inhaled via the air we breathe, and may become the underlying cause of endemic diseases (Appleton).

It has been recognized for many years that large areas of our planet contain endemic areas that are related to trace element excess, deficiency, and/or chronic poisoning. Thus, the health of billions of people around the globe can be affected by their geological environment. Many of these health-related problems have been associated with geological sources, e.g. contaminated drinking water, coal mining, volcanic eruptions, dust, etc., but also anthropogenic sources. In recent years, considerable interest has arisen in the assessment of the health risks posed by ambient geology. For example, the occurrence of endemic goiter and cretinism are both associated with iodine deficiency

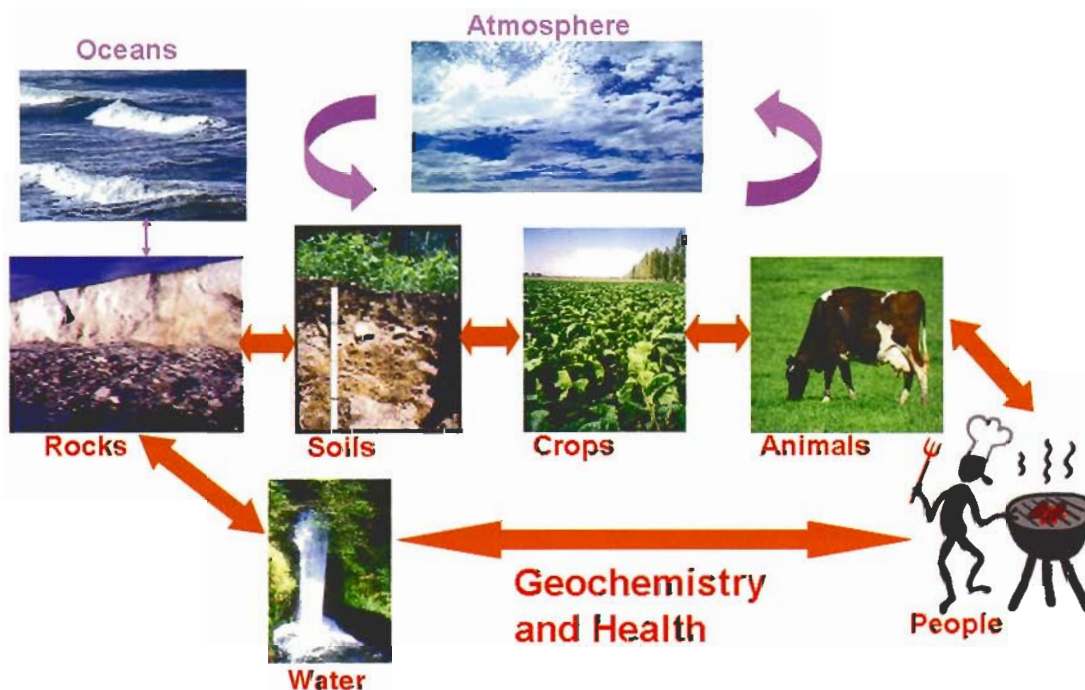
(Fuge). Selenium deficiency is related to cases of muscular dystrophy as well as the induction of endemic cardiomyopathy (Changshen Li, Fordyce). Excess fluorine in drinking water has also been associated with endemic dental and skeletal fluorosis in several geographical areas, e.g. India and Sri Lanka. Well-documented cases of chronic arsenic poisoning caused by arsenic contaminated drinking water are known in southern Taiwan, Chile, Argentina, Mexico, and China, and recently in West Bengal and Bangladesh where 70 million people are exposed to this problem (Centeno, Chin-Hsiao Tseng). The ash from volcanic eruptions can travel many times around the world, and recent satellite images have shown how dust from Sahara, Gobi and the Australian deserts has been carried by winds halfway around the world. Exposure to these dusts can cause a wide range of respiratory problems (Derbyshire).

Other topics addressed in the papers in this *Ambio* issue include the environmental and health problems associated with mining processes of e.g. coal (Finkelman, Orem).

Understanding the potential of Medical Geology for dealing with a wide variety of environmental health problems is of critical importance in order to bring together geoscientists and medical/public health scientists to address the problems caused by or exacerbated by geological materials such as trace elements, rocks, minerals, and water and geological processes such as volcanic eruptions and earthquakes. Before resources are committed to protect or clean-up the environment from man-made contamination, it would seem prudent to determine how much of the contamination merely reflects the preexisting natural background levels or is related to anthropogenic sources.

Hopefully, the following papers will shed further light on the complex issues involved.

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**Figure 1. Simplified schematic diagram of the cycling of chemical elements from the environment to man. The main geochemistry and health pathways are shown in red. Reprinted from F. Fordyce, Selenium Deficiency and Toxicity in the Environment. In: *Essentials of Medical Geology: Impacts of the Natural Environment on Public Health*, 2005, (ISBN 0126363412), Selinus et al., eds., with permission from Elsevier.**

# Epidemiological Transitions and the Changing Face of Medical Geology

## INTRODUCTION

Medical geology is defined as the study of the relationship between the geosphere and human health. Two recent books in this rapidly expanding field (1, 2) focus on current issues that generally involve exposure to toxic elements or compounds of direct geogenic origin, such as arsenic, mercury, and asbestos. A detailed understanding of these issues ultimately leads to scientifically based recommendations for public health interventions that decrease human morbidity and mortality. However, the relationship between our geological environment and our health antedates current public health practice by at least 200 000 years, when the first modern humans appeared.

Since that emergence of *Homo sapiens* in Africa, our species has undergone three epidemiological transitions, major changes in the pattern of our disease burden that result from steps in cultural evolution. Thus the advents of agriculture, industrialization, and globalization have led to the emergence of new diseases as well to the disappearance of others. It is the aim of this paper to trace the changing role of medical geology through these epidemiological transitions, thereby providing, for the first time, a historical perspective on the importance of this field.

## HUNTER-GATHERERS BEFORE THE EPIDEMIOLOGICAL TRANSITIONS

As hunter-gatherers, humans moved around in small family groups and were (still are in places) dependent primarily on the direct availability of unmodified environmental resources. Thus the major determinant of the disease burden was resource dearth, which could lead to hardship (lack of tools), exposure (lack of shelter or fuel), famine (lack of food), and local extinction (lack of healthy mates). Stone tools were vitally important for processing other resources, so much so that their availability could influence settlement, migration, and lifestyle. A good illustration of this is the dependence of early Aboriginal Australians on Eocene chert used in the manufacture of knives and scrapers.

When Aborigines first settled the Swan Coastal Plain on the southwest coast of Western Australia some 50 000 years ago, sea levels were lower, and there were exposed outcrops of Eocene chert to the west (3). This rock is ideal for producing cutting edges because of its conchoidal fracture pattern, and there were no other rocks in the area showing this fracture pattern to the same degree. As their chert quarries were submerged by rising sea levels late in the Pleistocene, chert artifacts became smaller and smaller because of an increasing dependence on the reuse of discarded chert artifacts. These finally disappeared from the local archaeological record about 5000 years ago, when the local Aborigines either succumbed through hardship or moved east, presumably driven by a need for a more suitable geological environment (3). In effect, this is an example of a geologically determined local extinction, an adverse health outcome that is clearly at the extreme of the disease burden spectrum to which our hunter-gatherer ancestors were subject.

As a further example, mineral resources were also a key determinant of colonization success in the peopling of the

Caribbean Islands. The first inhabitants were of both Central American (Casimiroids, using the Cuban countercurrent to reach Cuba and Hispaniola from the Yucatan peninsula about 4000 BC) and South American origin (Ortoiroids, using the south equatorial current to reach Puerto Rico from [then mainland] Trinidad about 2000 BC) (4). Culturally, both these peoples were preceramic and had only coarse stone tools; they lacked the knowledge of clays to produce pottery, and they did not have access to chert for the production of fine points and sharp edges. The Tainos—the dominant Indian group at the time of Columbus—on the other hand, had both pottery (improving food storage capability and reducing vulnerability to hurricanes) and chert (improving weapons, and found only in Antigua and Puerto Rico). These mineral resources had made it possible for the ancestors of the Tainos, migrating (invading) up the Antilles from Venezuela from about 500 BC, to supplant the preexisting Indian populations in what has been called the “First Repeopling” of the Caribbean (4). (The “Second Repeopling,” from 1492, was also significantly influenced by mineral resources, namely steel and gold, as readers of Diamond (5) will know.) Inevitably, the population health consequences for the supplanted peoples were disastrous.

By nature of the archaeological record upon which they are based, neither the Aborigine nor the Taino example provides a sense of the frequency and severity with which periodic famine would have affected health. Notwithstanding the dependence on mineral resources for food gathering, hunting, and storage, periodic famine is likely to have been the single most direct determinant of hunter-gatherer health and to have provided the drive in cultural evolution for the development of a more reliable approach to food availability. That new approach came in the form of agriculture.

## FARMERS AND THE FIRST EPIDEMIOLOGICAL TRANSITION

With the more reliable food supplies provided by agricultural production, people were able to settle villages, towns, and later cities. Population size and density increased, as did the intensity of animal contact, setting the scene for infectious disease to take over as the major contributor to the human disease burden. This changing demographic and epidemiological picture is known as the first epidemiological transition. The new food supply and associated sociocultural changes unfortunately also brought health problems of their own, and it is these that relate more directly to medical geology.

Variety in the diet had now been lost, often accompanied by a deficiency in the trace elements that are essential to health. In heavily leached soils, for example, iodine is deficient because iodine salts are generally very soluble. Iodine-deficient crops grew on such soils, and populations dependent on them were in turn iodine deficient. In inland areas this effect was exacerbated by lack of dietary intake of iodine from ocean fish and sea salt. In childhood, iodine deficiency resulted in cretinism, an intellectually disabling condition involving thyroid hormone (the function of which is iodine dependent). In the European Alps, where meltwater leaches valley soils heavily, entire agricultural communities were affected by cretinism until the

advent of improved food distribution and later iodized salt, both of which followed the industrial revolution. (For a recent review, see Fuge (6).)

In farming communities that remain largely dependent on local produce, other elemental deficiencies can also have direct impacts on health. Filip, one of the sailors on the ill-fated Swedish warship *Vasa* (sunk in 1628), was severely zinc deficient: he had a bone zinc content of only 10.5 ppm (<100 ppm is considered deficient), presumably the result of a diet excessively dependent on bread and porridge (7). This deficiency would arguably have predisposed him to prostate and other cancers, but it was the nature of public health issues in those days that he drowned clinging to the steering lever instead, aged only 20. There are many other examples, including selenium deficiency (8). Interestingly, though, our newfound dependence on agricultural production also introduced the possibility of exposure to some potentially toxic elements at above background levels. In a complex interplay between geology, culture, politics, and health, it is likely, for example, that Viking-age Icelandic farmers suffered adverse effects from ingesting the leachates of volcanic ash deposits.

Viking society was essentially a dispersed farming society (with a bit of raiding thrown in), and in 874 one Norwegian Viking farmer, Ingólfur Arnarson, established a homestead at Reykjavik. Many other settlers followed, often in an attempt to escape increasingly uncomfortable political conditions in Norway, most notably the centralization of power under Harald Fine-Hair (first king of a unified Norway, 890–942 AD). These farmers brought with them the skills and resources to reproduce their farming methods from Norway, including a strong tradition of dairying and grazing. Sheep did well and rapidly became the mainstay of the local economy, but these sheep also suffered from a strange disease that had never occurred in Norway: gaddur, an outgrowing of the teeth to the point of damaging the gums and cheeks of affected animals (Finnsson 1796, cited in Petursson et al. (9)). Gaddur was a sign of fluorosis, with severely affected animals also becoming stiff and lame as a result of joint involvement. These sheep had ingested fluoride-rich volcanic ash with either pasture or drinking water: Icelandic tephra can be particularly rich in fluoride, with calcium fluorosilicates ( $\text{CaSiF}_6$ ) adsorbed onto very fine ash particles with long dispersal potential. It would be surprising if this geological hazard had not also affected the human population, and there are several suggestions in the Icelandic historical literature that this may have been the case. One of the greatest Saga heroes, Egil Skallagrímson, had bone overgrowth arguably consistent with skeletal fluorosis, and many Icelanders affected by the 1783 Laki eruption demonstrated similar bone disorders (10, 11). Whereas hunter-gatherers might simply have moved on from ash-laden environments, farmers tied to their pastures and water supplies were left with little option but to ingest these geogenic toxins.

## **INDUSTRIAL SOCIETIES AND THE SECOND EPIDEMIOLOGICAL TRANSITION**

With industrialization came all the improvements in population health indicators associated with development: decreased child mortality, increased life expectancy, decreased birth rates and improved quality of life. These changes constitute the second epidemiological transition: an associated increase in the diseases of affluence, like cardiovascular disease and diabetes (which both result from inactivity and overnutrition). New technologies also led to the production of toxins at unprecedented rates, when for the first time in history human production sources exceeded ecological absorption sinks, and ecosystems as well as

the people dependent upon them were poisoned. Nowhere was this more obvious than in air quality.

Although fossil fuel (coal, peat) combustion was already affecting respiratory health in indoor environments, the resultant pollutants had, until now, usually not been as pervasive or persistent in their impact on human communities. With the industrial revolution, coal was burned at an unprecedented rate, and respiratory health was affected by outdoor air quality for the first time. Exposure to coal-produced  $\text{SO}_2$  and particulates ( $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$ ) now became chronic, and asthma and chronic obstructive pulmonary disease (COPD) developed into significant public health problems for the first time in our cultural evolution. Pollutants reached concentrations and persistence times that allowed new compounds to form under the influence of sunlight—the new phenomenon of photochemical smog. Outdoor air pollution had overtaken indoor air quality as the dominant exposure environment to compounds detrimental to respiratory health, and people started dying. Weekly mortality rates doubled during the “pea soup” fogs of London in the 1950s, with over 4000 excess deaths during one severe atmospheric inversion event that lasted for over a week in 1952 (12). Although emission controls have reduced this disease burden in the developed world, coal-generated “pea soup” smog is now killing people in the industrial centers of India and China. Cars exacerbated this problem not only by using yet another fossil fuel, petroleum, to generate  $\text{NO}_x$  and  $\text{O}_3$ , but by volatilizing metals such as lead. Lead was first added to petroleum as an antiknocking agent in the 1920s, and vehicle emissions have been the major source of airborne lead pollution ever since. In London in the early 1980s, the emission of lead was close to 10 000 tonnes per annum, with human exposure resulting through food, water, dust and direct inhalation. Convincing epidemiological evidence has since demonstrated that blood lead levels as low as  $10 \mu\text{g} (100 \text{ ml})^{-1}$  can adversely affect children’s IQ, and leaded petroleum is now banned or being phased out in most western countries.

Other metals were also dispersed and rendered bioavailable by industrial processes. In Minamata Bay, Japan, mercury of industrial origin bioaccumulated in local food chains. Produce from the bay poisoned the nervous systems of people in local fishing communities, resulting in a disease that now bears that bay’s name. In Bangladesh, wells driven into arsenic-laden rock strata are poisoning millions through the drinking water supply, creating one of the biggest public health engineering disasters in history. We will revisit this example below, and these and other geogenic toxins will also be discussed in more detail by later presenters in the symposium.

Less direct (but arguably as important) geological effects of industrialization can be seen at the global scale. Mechanized agricultural overproduction has led to desertification, producing vast sources of globally dispersed dusts that may pose a significant pathogen dispersal risk (13). Soil salinization has led disease-carrying coastal mosquitoes to spread inland, increasing the risk of arbovirus infections in populations not previously exposed to these species (14). Global environments (including geological environments) are being altered at an unprecedented rate, and it has been argued that such changes are contributing to what will be the third epidemiological transition (15).

## **GLOBALIZATION AND THE THIRD EPIDEMIOLOGICAL TRANSITION**

If large populations continue to overexploit environmental resources at the current (or at an accelerating) rate, it is inevitable that ecosystems will increasingly fail to provide those services upon which the health of human populations depends. Many would argue that the emergence and reemergence of some

diseases is already a reflection of unsustainable resource use (16), and new disease outbreaks have been interpreted as bioindicators of ecosystem disruption (17). The changes in disease burden associated with the disruption of health-sustaining ecosystem services have been described as the third epidemiological transition (18), and because geochemical cycles underlie most ecosystem services, an understanding of medical geology is again integral to solving environmental health problems during (and after) this transition.

The ongoing impacts of infectious disease are still actively discussed in both the popular and scientific media, and there is an increasing realization that geological factors underlie the current emergence and reemergence of many of these (19). Lyme disease for example, a debilitating infection with the tick-borne pathogen *Borrelia*, has recently emerged as a major public health problem in the United States. The vector ticks, *Ixodes scapularis*, are present on alfisol-type soils of sandy or loam-sand textures overlying sedimentary rock, and are absent from areas with acidic soils of low fertility and a clay soil texture with Precambrian bedrock (20). Ecosystem disruptions resulting from human overexploitation or resources have led to Lyme disease becoming an "emerging infectious disease" only in areas with the former soil type. Many other human pathogens are either directly or indirectly dependent on soil ecology (21), and therefore also have the potential to emerge or reemerge as public health problems in areas where anthropogenic disruptions to soil ecology take place.

The mass poisoning of people on the Indian subcontinent by arsenic-laden drinking water is another example of disease emergence as a result of human overexploitation of environmental resources. The unsustainable use of surface water and abstraction of groundwater, ultimately a result of population pressure, led to the inappropriate sinking of new wells into geologically unsuitable strata. Shallow aquifers in alluvial and deltaic sediments now deliver drinking water to tens of millions of people through millions of domestic bores, over half of which exceed the World Health Organization (WHO) arsenic guideline of  $10 \mu\text{g L}^{-1}$  (22). With the causal relationship between skin changes (hyperkeratosis, squamous cell carcinoma, basal cell carcinoma) and arsenic exposure now well established (23), it is clear that the unsustainable use of geological resources is already contributing significantly to the global disease burden—a disease burden that is becoming increasingly consistent with the changes expected from a third epidemiological transition.

The creation of a global geochemical database has been proposed as one means of providing a frame of reference on which to base interpretations of change and recommendations for the sustainable use of the Earth's land surface (24). Medical geology could, in this context, inform land use planning on the broadest scale, including mining, agriculture, and waste disposal. On this broadest planning scale, there is also a relationship between fossil fuel use, global warming, and increases in climate-related morbidity and mortality—arguably the greatest challenge that will face environmental health practitioners for several generations to come (25, 26).

## CONCLUSION

Before the first epidemiological transition, a Neolithic medical geologist might have analyzed the health gain attributable to the discovery and use of particular geological resources. In agricultural and later industrial societies, medical geologists (albeit using different labels) made recommendations about

maximizing soil yields and minimizing toxic pollution and human exposure. The medical geologist of the future will be a multidisciplinary, able to span a breadth of geological (basic, applied, environmental), medical (clinical, epidemiological, sociological), and political sciences. As an emerging science, medical geology will provide a strong collaborative framework to start addressing environmental health problems including those that may arise from the third epidemiological transition will throw at us.

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# Iodine Deficiency: An Ancient Problem in a Modern World

## INTRODUCTION

Iodine has long been known as an essential element for humans, and for mammals in general, where it is concentrated in the thyroid gland, being a vital component of the thyroid hormone thyroxine. Deprivation of iodine results in a series of iodine deficiency disorders (IDD), the most commonly recognized of which is endemic goiter, a condition where the thyroid gland becomes enlarged in an attempt to be more efficient. Iodine deficiency during fetal development and in the first year of life can result in endemic cretinism, a disease that causes stunted growth and general development, together with brain damage. However, although these 2 diseases are easily recognizable, the more insidious problem is that iodine deficiency impairs brain development in children, even when there is no obvious physical effect; indeed, it has been suggested that iodine deficiency is the most common preventable cause of mental retardation.

Endemic goiter and cretinism, together with related IDD, have long been recognized as serious health problems, and, consequently, much work has been carried out on the etiology and geographical distribution of these diseases. Although it has been suggested that other elements and factors may be involved, it is generally agreed that the primary cause of IDD is a lack of iodine in the diet.

Endemic goiter appears to have been identified by the ancient Chinese, one Chinese medical writer from the 4th century AD noted the use of the brown seaweeds *Sargassum* and *Laminaria* (which are now known to be very iodine rich) for its treatment (1). However, there are many earlier records in ancient literature of seaweeds and burnt sea sponges being used in the treatment of endemic goiter possibly from as early as 2700 BC (1). Iodine was discovered by the French chemist Bernard Courtois in 1811 when he accidentally added concentrated sulfuric acid to the seaweed *Fucus vesiculosus*, one of the seaweeds used in goiter treatment. It was soon realized that iodine was the active ingredient in the treatment, being identified as an essential element in human nutrition, consequently, thyroxine was discovered and identified in 1919.

Despite this early recognition of the role of iodine in endemic goiter and related disorders, it is apparent that IDD is still affecting large numbers of people worldwide, with some estimates suggesting that around 2 thousand million of the world's population are at risk. Before the middle of the 20th century iodine deficiency problems affected virtually every country (2). Subsequent to the addition of iodine to the diet as a prophylactic, mainly through iodized salt, IDD had more or less been eradicated from the developed world by the 1970s and were generally regarded as diseases of the poor. Although a large percentage of those currently at risk of IDD are located in the developing world, over the last 15 years or so it has re-emerged in some of the more affluent countries of Western Europe, such as Austria, Belgium, Denmark, Germany, and France, and is also re-emerging in other countries, e.g., Australia. Based on the data of Dunn and van der Haar (3), Figure 1 indicates the general global distribution of IDD.

## IODINE GEOCHEMISTRY

A brief look at iodine geochemistry reveals that it is unique among the elements. Most elements in soil and water are derived from weathering of the lithosphere; in general, that is not the case with iodine. Most of the iodine in the pedosphere and the hydrosphere derives from the marine environment via the atmosphere. Iodine is very low in the lithosphere,  $0.25 \text{ mg kg}^{-1}$  on average, with sea water being the major terrestrial reservoir of iodine, containing approximately  $60 \text{ mg L}^{-1}$ .

The major feature of iodine geochemistry is its volatility. It is volatilized from the sea in 2 main forms, firstly as elemental iodine, because of the action of ultraviolet light and possibly ozone. Secondly, it is known that it volatilizes as methyl iodide,  $\text{CH}_3\text{I}$ , and other organic iodine species, most probably because of biological involvement. In these gaseous forms in the atmosphere, it is carried onto the terrestrial environment, where it is deposited onto soils by wet and dry precipitation. So most terrestrial iodine derives from the marine environment by way of volatilization, so that soils in coastal areas are strongly enriched in iodine compared with those from areas remote from the sea. Subsequently, iodine can be revolatilized from soils and terrestrial waters.

Iodine was the first trace element recognized as being essential for humans; why then do IDDs persist and reoccur in affluent countries? This author suggests that the reason is that there is a widespread misunderstanding about iodine geochemistry and pathways into the biosphere and, ultimately, humans. There are 2 generalizations with regard to iodine biogeochemistry, firstly, as a consequence of its derivation from the sea, it has been suggested that only areas remote from marine influence are problem areas for IDD. Although central continental and rain shadow areas of high mountain ranges are seriously affected by IDD, it is very questionable that areas close to marine influence are unaffected. The second generalization is that plants or crops provide the major dietary source of iodine; this is also very questionable.

A brief look at the data for iodine distribution in soils confirms that it is strongly enriched in coastal soils, compared with those inland (4). However, traverses of topsoil samples taken at increasing distances from the coast reveal that the strong iodine enrichment is confined to a fairly limited zone close to the coast. From traverses from the west coast of Wales, United Kingdom (5), and Morocco (6), it is apparent that strong soil-iodine enrichment is limited to about 100–120 km from the coast. Beyond this distance concentrations of iodine are close to the values found in central continental regions. Previously unpublished data for a traverse inland from the west coast of the Republic of Ireland, illustrated in Figure 2, also demonstrates this phenomenon.

The iodine content of soils is governed not only by its supply, generally reflecting proximity to the coast, but also by the ability of the soil to retain the added iodine. Iodine retention in soils is strongly influenced by soil type. Thus organic-rich soils are frequently enriched in iodine, with peats having some of the highest values recorded for iodine in soils. Iron-rich and clay-rich soils are enriched in iodine, whereas sandy soils and waterlogged soils are generally depleted. It is also apparent that

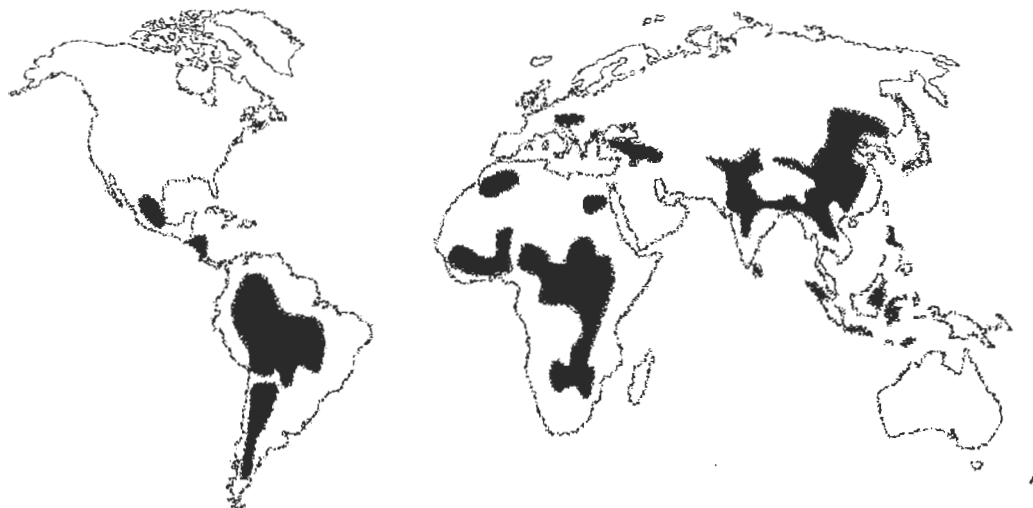


Figure 1. Global distribution of iodine deficiency disorders (modified from Ref. 3).

soils over limestone are generally richer in iodine compared with soils overlying other lithologies in the same regions.

### IODINE UPTAKE BY PLANTS

The iodine content of soils from some areas of the United Kingdom that have historical records of IDD are listed in Table 1. It is of interest to note that many of these are relatively high in iodine. So why do we find iodine deficiency disorders in areas with relatively high soil iodine?

The major problem is that iodine is very strongly held in soil, less than 10% and generally much less than 10%, is water soluble. There is no correlation of iodine in soils with plants growing on those soils, and it is generally agreed that the soil-plant transfer factors for iodine are very low. Both anionic forms of iodine, iodide ( $I^-$ ) and iodate ( $IO_3^-$ ) are very large ions. Despite the large size of these anions, it has been shown that iodine is taken into the roots of plants with  $I^-$  being more readily incorporated than  $IO_3^-$ . Even so, it has been shown that whereas iodine gets into the roots, it is not translocated into the aerial parts of the plants. However, it has been shown that plants can take in iodine through their aerial parts through the stomata in the leaves, this being thought to be a far more important source than root uptake. It is likely, therefore, that volatilization of iodine from soils is a very important pathway into plants and that if such volatilization does not occur, then the plant is deprived of its major source of iodine.

It is of interest to note that many goiter endemias have been recorded in regions underlain by limestone, such as the Peak District of Derbyshire, England, where iodine in soils is relatively enriched (Table 1). Frequently, soils in limestone areas are circum-neutral to alkaline, and under these conditions iodine is unlikely to be volatilized. Similarly, in England and Wales, some goitrous areas occur where peaty soils predominate, again these are high iodine soils (Table 1). It is likely that peaty soils retain iodine very tightly and so little is available to be volatilized.

### SOURCES OF DIETARY IODINE

It is traditionally perceived that vegetables and crops are the sources of iodine for humans. However, plants are generally low in iodine, and vegetarian diets have been singled out as being iodine deficient. In general, animal produce is a better source of dietary iodine than plants. Until fairly recently, the use of iodophores, iodine-containing disinfectants, in the dairy industry resulted in dairy produce being a very major source of dietary iodine. However, iodophors are not used to the same degree currently, so that dairy produce is not as enriched in iodine. Despite this, dairy produce is still an important source of dietary iodine, because cattle feeds are supplemented with iodine.

It is also worth pointing out that grazing animals are likely to take in appreciable quantities of iodine because iodine volatilized from soils is deposited on the surfaces of vegetation rather than incorporated into the plant. Likewise, soil splashes onto leaves and soil inadvertently consumed by animals is going to be a richer source of iodine than the vegetation growing on it. This has been demonstrated in New Zealand and Tasmania, where sheep found to be ingesting soil containing only  $1 \text{ mg kg}^{-1}$  of iodine did not suffer from iodine deficiency.

Seafood is generally a rich source of iodine and, in particular, seaweed. In some countries, such as Japan and Iceland, where there is a high consumption of seafood, some populations have been found to be consuming too much iodine and, as a result, have suffered iodine thyrotoxicosis. In some regions of the world, drinking water derived from groundwater is rich in iodine and can constitute a major source of dietary iodine; but, in most cases, water is a poor source of dietary iodine.

It has been suggested that burning of high iodine coals in some rural iodine-deficient areas of China has impacted populations living in these areas, resulting in a lower incidence of IDD (7).

The most important source of dietary iodine, and the major reason for the drop in IDD in the mid 1900s, is iodized salt.

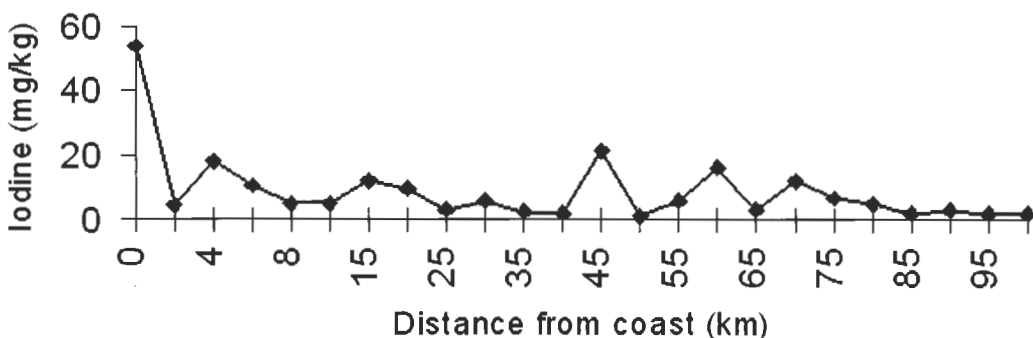


Figure 2. Iodine in topsoils in a traverse inland from the west coast of Ireland.

**Table 1. The iodine content of soils from areas of England and Wales with a history of endemic goiter.**

Area	Range (ppm)	Mean
Peak District, Derbyshire	2.6–26	8.2
North Wales	3.4–14.5	9.8
Dartmoor	10–35	21
North Oxfordshire	4.8–11	6.2

However, in modern diets consumption of relatively high quantities of salt is regarded as somewhat harmful, resulting in high blood pressure. In addition, in the affluent world, there has been a general move away from preparing all meals in the home. It is now commonplace for processed foods to be purchased, and such foods contribute the major part of salt in the diet. Such foods, in general, are not prepared with iodized salt. Hence, a very important source of dietary iodine is minimal in modern diets. Added to this, another important source of dietary iodine is dairy produce, and current health fads suggest that one should not eat too much dairy produce, because it is harmful. So that there are a large numbers of people in the developed world now who drink very little milk and consume little or no dairy produce and consume little iodized salt, thereby making their diets very low in iodine. It is apparent that with modern diets in affluent countries IDD are likely to be become even more common.

## CONCLUSIONS

It is perhaps worth noting that humans evolved from marine life forms and that the marine environment is enriched with iodine. Early terrestrial animals lived close to the sea, but, on moving

inland, they moved from the major source of iodine. Once they got further than 100 or so kilometers from the sea, the marine source of iodine was cut off. Humans evolved in areas fairly remote from the sea, and, as a consequence, it is probable that iodine deficiency is the norm and most diets are marginal. It has been suggested that a third of the world population are at risk of IDD; the author suspects that a great deal more than that are at risk and if modern dietary trends continue an even greater upsurge of iodine deficiency disorders will occur in the affluent countries of the world.

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# Natural Minerogenic Dust and Human Health

## DUST SOURCES

Atmospheric aerosols include gases and liquids, as well as solid particles. They include material derived from both oceans and landmass, as well as particles that form within the atmosphere, such as sulfates. Solid particles entrained in the atmosphere by detachment from poorly vegetated surfaces (the process of deflation) include, for example, rock and mineral dust, fine mineral aggregates, fibrous minerals, fibrous organic materials, and sea salt. The burning of vegetation (biomass) yields black carbon, which adds to the opacity of the atmosphere. Smoke plumes from fires, both natural and anthropogenic, are often carried thousands of kilometers from their sources, so increasing the air pollution hazard. In addition to the strongly seasonal inputs from the world's drylands, mineral-dust loading of the atmosphere is also enhanced by injection of fine volcanic mineral particles (*tephra*) containing variously toxic minerals.

This paper considers only those dusts that are derived naturally from the land surface, especially in and around the world's drylands. Anthropogenically generated dusts (such as those derived from industries, vehicles, etc.) are not considered here, although mention is made that both inorganic and organic toxic substances may become attached to natural atmospheric dusts, including toxins of human origin.

Atmospheric aerosols also influence the chemistry of the troposphere, including the proportion of ozone. Particle size and chemistry of the dust load affect air temperatures (by varying absorption and scattering of solar radiation). Given the present global warming trend, progressive desertification, and human actions that continue to increase the atmospheric dust loading, the intimate relations between aerosols and the global environment have obvious implications for future climatic change (1), and yet further indirect effects on human health around the world.

Detachment of mineral dust from the ground surface ("deflation"), and its entrainment and transport by the wind is a function of several variables, including wind speed (notably the critical wind speed or threshold velocity required to dislodge particles), the degree of atmospheric instability, the size and shape of the particles, the roughness and moisture content of the land surface, and the degree of particle exposure. The clay-size ( $<2 \mu\text{m}$ ; Fig. 1) component of soils and sediments is not readily detached from a land surface by the wind as individual particles because of the high interparticle cohesive forces typical of such colloidal materials. Entrainment of these finer particles usually occurs in association with the coarser (silt-sized) grains,

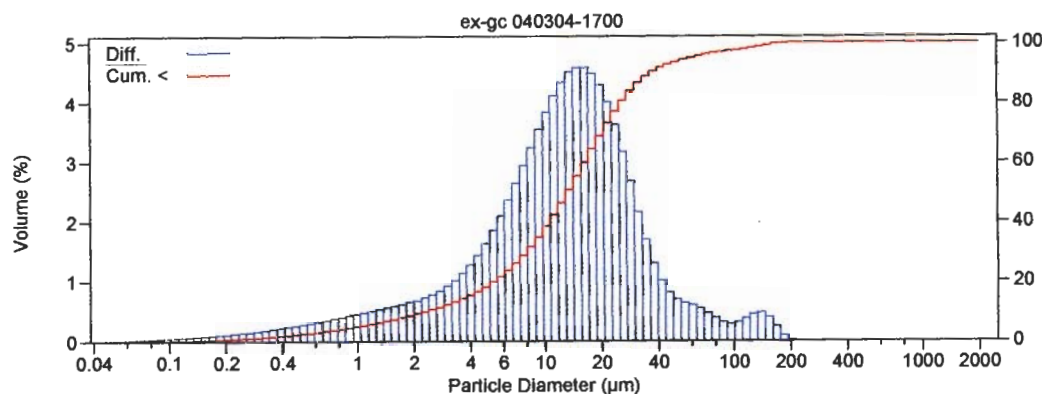
as well as in the form of coarse or medium silt-sized aggregates made up of variable mixtures of fine silt and clay-grade particles. Once entrained, however, fine dust particles may travel a thousand or more kilometers before being deposited, some of the finest particles being transported as much as 20 000 km from their source (2). Travel distance is largely a function of particle size and atmospheric conditions, the coarser fractions being deposited much closer to their source. The medium and coarser fractions of such dust (mainly in the silt range:  $2\text{--}63 \mu\text{m}$ ) may accumulate to form the sediment type known as *loess* (3, 4). Loess is made up of wind-lain geogenic dust, which is subject to varying degrees of postdepositional alteration, particularly by the processes of weathering and soil formation. Loess has been accumulating on the continents, especially Eurasia and the Americas, for millions of years. Its susceptibility to erosion by both wind and water, especially along desert margins and on degraded dryland surfaces, make it a secondary source of wind-blown mineral dust, as mentioned further on.

Dominant dust sources around the world are almost wholly in or adjacent to the great drylands of the northern hemisphere. The greatest of these includes a broad swathe of land across North Africa, the Middle East, northwest India, and central and eastern Asia—from the western Sahara to the Yellow Sea. Other notable sources are found in the Great Basin of the United States and, in the southern hemisphere, east-central Australia, central and northern Argentina, and parts of southern Africa.

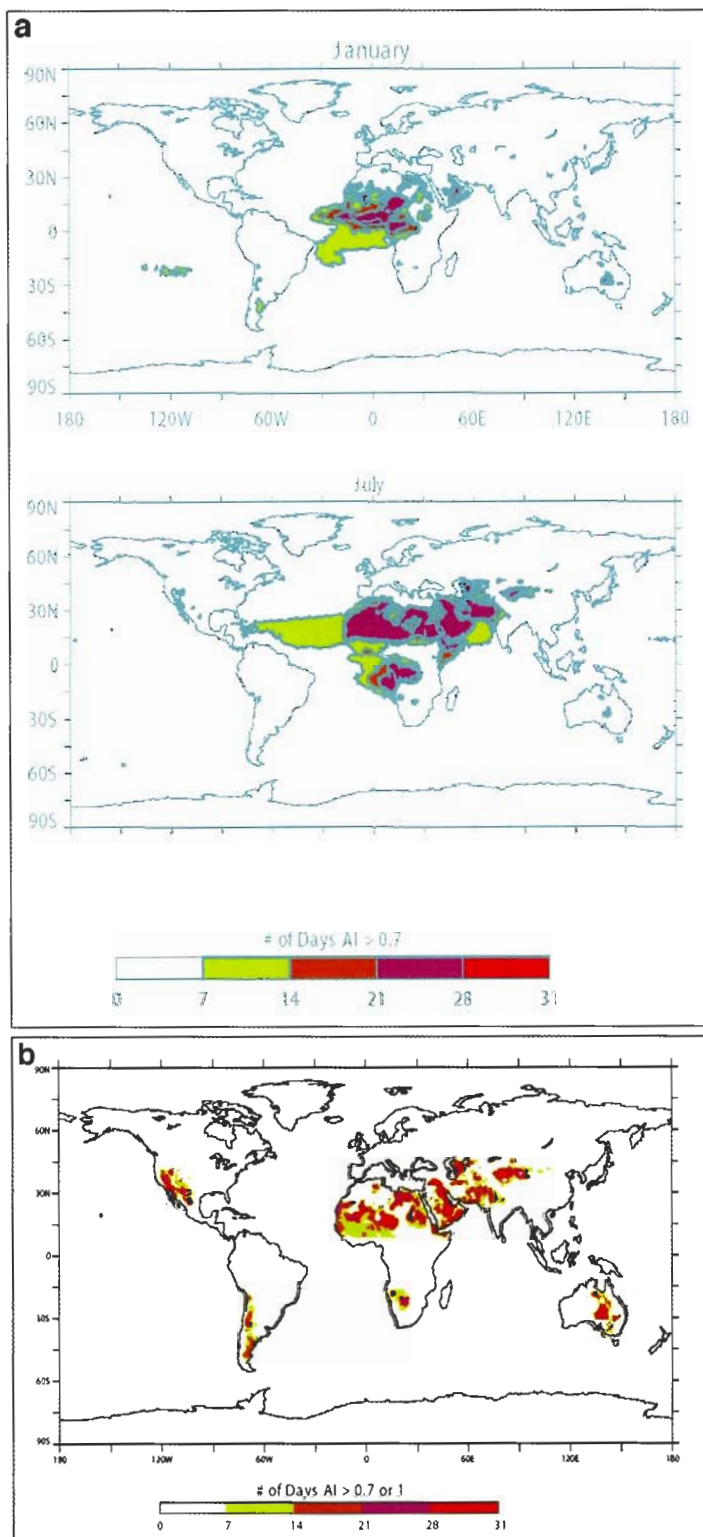
In both North Africa and China, dried-out former lake beds are a major source of fine, readily deflated mineral dust (e.g., 5, 6). The Bodélé depression [Chad, North Africa (7)] and the numerous lake depressions in northern China and central Asia are major dust sources of global significance (Figs. 1 and 2).

Saharan dust, driven by the northeast trade winds, takes about a week to cross the Atlantic Ocean, reaching northeastern South America in the (northern) late winter and spring, and the Caribbean, Central America, and the southeastern United States in summer and early autumn (8) ( Fig. 2 ).

The midlatitude deserts of Asia are a source of substantial airborne dust, especially during spring and early summer. The two major Chinese dust sources (Mongolia and the Tarim Basin–Taklamakan Desert) are of global importance, fine dust from both these regions having been traced to North America, Greenland, and Europe. Driven in the winter half year by large "Siberian High" pressure cells, locally easterly winds flow around the southern flank of the seasonal high pressure cell that



**Figure 1. Modal and cumulative percentage volume curves for natural Saharan dust deposited on the island of Gran Canaria in March 2004. The particulate matter (PM) 10 fraction makes up almost 40%, and the PM 2.5 almost 20% of the total volume. (Courtesy of Kenneth Pye.)**



**Figure 2. Atmospheric dust monitoring using orbital spectrometry. The Total Ozone Mapping Spectrometer (TOMS) is sensitive to a range of ultraviolet (UV)-absorbing aerosols such as mineral dust, volcanic ash, and black carbon from fossil-fuel combustion sources and biomass burning. The UV surface reflectivity is typically low and nearly constant over both land and water; this allows TOMS to detect aerosols over both continents and oceans. The UV spectral contrast is used in a non-quantitative way as an absorbing aerosol index (AAI).**

**a. Global distribution of the occurrence frequency of relatively high TOMS AAI values for January and July 1980–1992.**

**b. Long-term dust storm frequency, showing a distribution of major sources closely similar to other data sources. Sources occur in all continents except Europe and Antarctica (5).**

develops over the Taklamakan Desert, and are vigorously uplifted into the upper troposphere westerlies as they come up against the western Kunlun, the Pamir, and the western Tian Shan ranges (all with peaks about 7000 m above sea level). Dust from the Mongolian sources is carried in a more directly west to northwesterly air stream, accounting for the severe late winter and spring dust storms that affect densely populated north-eastern China [Fig. 3; see also Fig. 10 in Ref. 9)]. Although airborne dust volumes have increased in the past 30 years or so as a result of increased human settlements and some imprudent farming practices, especially along the southern margins of the northern Chinese deserts (Badain Jarain, Wulanbuhe, Mu-Uu, and Onzin-Daq), the process is a natural one with a history going back at least 8 million years. The loess formation, which exceeds 300 m in thickness in several parts of the North China, is impressive evidence of sustained, semicontinuous deposition of the coarser airborne dust fractions (sandy silt and silt) for at least the past 2.6 million years.

The long-term global dust storm frequency closely reflects the distribution of the major dust sources. The annual mean number of “dust days” (defined as reduction in visibility by dust to <1 km) is impressive; e.g., 80 in southwest Asia; more than 30 in the Tarim Basin (Taklamakan Desert), the Hexi Corridor, and the Loess Plateau of China; about 30 in parts of North Africa; and about 20 in the northwest Indian subcontinent (10). Dust storm frequency may be set to increase in some parts of the world if current trends in climate and other environmental changes continue.

Dust palls, rich in very fine mineral dust, occur at both regional and continental scales. Although measurable palls occur throughout the year in some regions, including Middle Asia, Ladakh (NW India), and all of North China (where the exposed population has been estimated at 24 million), there remains much to be learned about the physical, mineralogical, and geochemical characteristics of ambient mineral dust in the context of assessing the disease burden upon exposed human communities. Determination of natural dust sources and concentrations on a regular basis is needed to establish background levels that can serve as a datum for detailed assessment of human and animal exposure levels. Quantitative information on naturally occurring background levels of potentially toxic aerosols is generally sparse, underlying the need for much more detailed physical, chemical, and mineralogical characterization of atmospheric dust.

## **PATHOLOGICAL EFFECTS OF INHALED MINERAL DUST**

Pathological effects arising from inhalation of mineral dust varies with several factors, but the size, shape, and chemical and mineralogical composition of dust particles, the length of exposure of the subject, and certain lung functions are of notable importance.

Inhaled coarse mineral particles (>10  $\mu\text{m}$ ) are commonly lodged in the upper respiratory tract and are rejected by expectoration, but they may constitute a health risk if the mineralogy is toxic, regardless of where the grains lodge in the respiratory system. The respirable fraction (particles <10  $\mu\text{m}$ , the first “PM standard” of the US Environmental Protection Agency) may remain suspended in the atmosphere for some length of time (weeks); the fraction of the dust  $\leq 4 \mu\text{m}$  that penetrates more deeply into the finer lung passages may cause silicosis, asbestosis, and other lung conditions (Fig. 1). Mineral dust finer than 3  $\mu\text{m}$  found in lung tissue from one Chinese postmortem subject made up about 75% by weight of the total dust burden in the lungs (similar grain size to the second “particulate (PM) standard” of <2.5  $\mu\text{m}$ ). The denser the

ambient dust and the longer the exposure, the higher are the rates of chronic respiratory disease and associated death rates.

Inhalation of the finer ( $\leq 4 \mu\text{m}$ ) fractions of mineral dust eventually leads to deposition in the pulmonary alveoli where chronic lung disease is initiated. Some types of inhaled particulates are degraded by macrophages (mononuclear phagocytes in the lung alveoli), but many are highly resistant to this process and persist in the lungs. Some resistant particulates appear to cause no problems, but others stimulate fibroblastic cells (secretory cells of connective tissue) to deposit collagen, a protein making up the white fibers of skin, cartilage, and all connective tissue. Although the precise nature of the pulmonary response to mineral dust particles is complex, a number of factors are considered to influence potential toxicity. These include the presence of specific minerals within the respirable fraction, the shape of particles (which influences clearance from the lungs), the presence or absence of mineral coatings, and particle surface characteristics including surface area and surface chemistry including the potential to generate free radicals (which can instigate disease by causing damage to lung tissue by abstracting electrons from DNA (11).

The dominant mineral in Eurasian dust is quartz ( $\text{SiO}_2$ : "free silica"). The measured quartz content in major dust storms is very similar (60.95% in North Africa; 60.26% in China), closely matching the mean value for the Earth's crust (58.98%). Silica is a highly fibrogenic agent in lung tissue, a process that is very different from the granulomatous reaction attributed to many other nondegradable grains.

There is evidence that response varies with the species of silica inhaled. Some forms of biogenic silica (e.g., diatoms and phytolith fragments) with diameters  $< 10 \mu\text{m}$  are common in, for example, Saharan dust, but are generally considered to be benign.

Radiographically visible fibrosis may take years to appear. Radiographic diagnosis of silicosis is made with confidence only after the appearance in a patient's lungs of silicotic nodules 2–5 mm in size. Continued dust exposure leads to an increase in nodular size and number. Eventually, nodules may cover much of the lung, the nodules sometimes coalescing to form conglomerate shadows, a stage often called progressive massive fibrosis (12).

The group of lung diseases known as pneumoconiosis includes silicosis and asbestosis. Silicosis arises from prolonged inhalation of free silica; it is a seriously disabling disease, being progressive and incurable. Silicosis has attracted considerable attention as probably the most widespread of the *occupational* diseases, but nonoccupational silicosis has been relatively little studied even in regions with large populations exposed to massive, ambient dust concentrations. Asbestosis is a degenerative fibrosis of the lung resulting from chronic inhalation of asbestos fibers. Asbestos is a group of fibrous silicate minerals that includes extremely fibrous serpentine (chrysotile) or amphibole minerals (crocidolite, amosite, tremolite, actinolite, and anthophyllite) found in a wide variety of geologic environments. Although not covered by the term "asbestos," the mineral erionite, a fibrous zeolite, is also known to cause asbestosis and related conditions.

The impact of airborne mineral dust may be exacerbated by the presence within fine dust particles of bacteria, fungi, and other microorganisms (13). The global extent of the fine dust transport system has been implicated in intercontinental transport of microorganisms with the potential to damage plants and animals, including human subjects (14–16). Although susceptible to destruction by ultraviolet radiation, a proportion of the included microorganisms may survive in cavities and cracks within suspended dust particles. Deteriora-

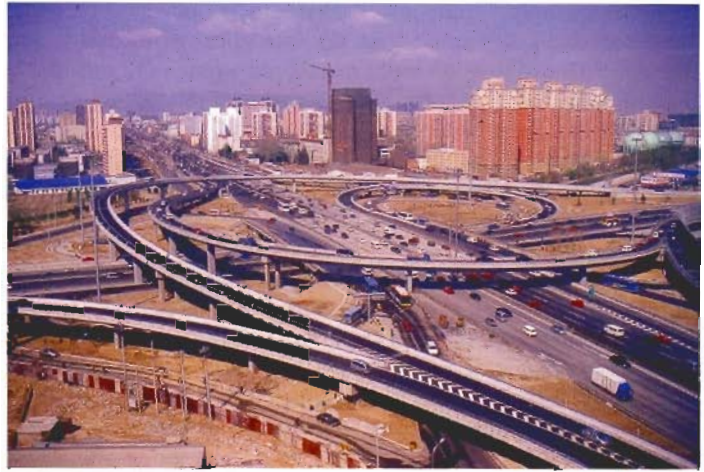


Figure 3. Before and during a Mongolian dust pall over Beijing, April 2003. Photograph by the author.

tion of coral reefs in the Caribbean has been attributed to fungi (*Aspergillus sydowii*) transported by North African dust (17).

Notwithstanding increased awareness and understanding of the main pathways and pathological impact of naturally occurring dusts, including a number of case studies such as those illustrated in the following section, information on the disease burden arising from exposure to naturally occurring dusts in different populations around the world remains sparse. Specifically, the strength of the relation between known high frequency atmospheric dust concentrations and the type and frequency of community illness requires critical assessment, especially in a number of perceived high risk environments. Current trends in climate change and aridification make this a matter of some urgency, especially in the drylands along the margins of the middle latitude desert zone that extends across the Old World from West Africa to the Yellow Sea.

## SELECTED CASE STUDIES

### Nonindustrial Silicosis

Nonindustrial silicosis has long been recognized in northeast Africa and the Middle East, where it is referred to as "desert lung syndrome," the earliest known cases being found in some ancient Egyptian mummified bodies (18). Nonindustrial deposition of silica in human lung tissue was first reported in living populations in a study of three inhabitants of the Sahara Desert more than half a century ago (19). Typical autopsy results showed a high content of fine ( $< 3 \mu\text{m}$ ) silica dust.

A radiographic study of 54 Bedouin people in the Negev Desert strongly suggested that the incidence of fibrosis is age related, with progression more notable in women (13 out of 22) than in men (only 4 out of 32), perhaps related to greater exposure in and around the family tents (20). Other findings from different parts of North Africa include radiological evidence of multiple micronodules in reticular disposition scattered throughout the lungs, and considered to be consistent with silicosis (21).

More recently, the human health impact of Saharan dust storms (local Spanish: *calimas*) has been recognized in the Canary Islands (Las Canarias), where the respirable dust percentage is high, some 35%–40% by volume being finer than 10  $\mu\text{m}$  and about 20% finer than 5  $\mu\text{m}$ . This is known to give rise to cases of breathing disorders, including asthma, in autumn but especially in the late winter to early summer season. Dust samples taken regularly during *calimas* at several sites on the island of Gran Canaria, including a summit site (1930 m) include measurable contents of several elements implicated in lung disease. Silicon is dominant in all cases [quartz > 60%: (22), Gelado et al., unpublished].

Research studies undertaken in Ladakh are of particular interest (23–25). This is a region without any mines or industries, but one in which dust storms are frequent. Mineral dust found on the upper surfaces of wooden roof beams of Ladakhi houses is all finer than 15  $\mu\text{m}$ , more than 25% by weight being finer than 1  $\mu\text{m}$ ; the silica content is >60%. Study of necropsy lung tissue samples from villagers revealed heavy dust deposition with abundant hard, 1–3 mm diameter nodules and a lymph node largely replaced by hyaline collagenous nodules, a classic feature of silicosis. More than 20% of the mineral dust extracted from the lung tissue consisted of quartz; bulk chemical analyses yielded 54% elemental silica and 19.2% aluminium. In the study by Norboo and others (24), radiographic evidence was derived from an equal number of men and women between the ages of 50 and 62 years in two villages at different altitudes (3200 and 3500 m above sea level). These data revealed important differences evidently arising from the higher dust concentrations found in the lower of the two villages. Several cases of progressive massive fibrosis were found in the lower village, with none in the upper village, suggesting that silicosis may cause appreciable morbidity at lower altitudes in this environment.

The large population subjected to frequent dust storms in north China probably includes substantial numbers of people with nonoccupational silicosis, although the number of available published studies is sparse.

One published study in China (26) involved a group of 395 people (294 men and 101 women) in two communes in the middle of the Hexi Corridor, Gansu Province. Lying between the stony desert (Mongolian: *gobi*) of Inner Mongolia to the north and the 700 km long Qilian Mountains and Tibetan Plateau to the south, the Hexi Corridor is subject to dense, and often violent dust storms driven by strong westerly winds associated with the Siberian high pressure cell, especially between spring and early summer. Measured dust concentrations reached 42  $\text{mg}/\text{m}^3$  at outdoor sites, rising to 200  $\text{mg}/\text{m}^3$  indoors, with a free silica content of 61%. A 7% incidence of pneumoconiosis was found in the tested population, but no significant difference in incidence was found between the sexes, despite the much higher dust concentrations found inside domestic dwellings. A clear increase in incidence with age was found, however, with pneumoconiosis occurring in more than 40% of subjects over 40 years of age. An extension of radiographic studies to domestic animals showed that even the lungs of camels are affected by silicosis in this region. The situation in the Hexi Corridor is complicated by the presence of

industries associated with some of the main cities and towns, adding fly ash and potentially toxic elements, including Cu, V, Pb, Zn, and As to the dust burden (27).

### Silicosis: Link to Tuberculosis

Silicosis has some deleterious effects upon the immune system. Some rheumatic diseases, as well as chronic kidney diseases, also show higher than average incidence in individuals exposed to silica, and such increased susceptibility of subjects to several mycobacterial diseases is, to some extent, due to impaired function of macrophages in silicotic lungs.

Impairment of the immune system may give rise to a reduction in the ability of macrophages to inhibit growth of tubercle bacilli. Nontuberculosis mycobacterial infections (involving intercellular bacterial parasites) may occur, but long, continued exposure to silica has been linked to increased rates of infection with pulmonary tuberculosis, a notable public health problem in many developing countries. The causal relation between silicosis and tuberculosis has been demonstrated in occupational health studies in which South African gold miners with silicotic lungs were shown to be more susceptible to tuberculosis.

Tuberculosis seems an unlikely disease to be found in drylands, because sunlight and aridity are antipathetic to the development of tubercle bacilli, and droplet transmission of pulmonary tuberculosis is favored by *lack* of sunlight, higher humidity, and overcrowding. However, data from the Thar Desert in northwest India show a prevalence of tuberculosis in the desert areas of Rajasthan that is some 25% higher than in the nondesert parts. Radiographic evidence of nonoccupational silicosis in desert people thus offers some support for the view that silicosis may be an important factor in the higher prevalence of tuberculosis in some deserts (28).

### Nonindustrial Asbestosis

Natural release of asbestiform minerals from the host rock occurs by the processes of weathering and erosion, the fibers frequently becoming concentrated by overland flow of surface water such as sheetwash and rilling. In seasonally dry climates, concentrations of fibers dry out and so become susceptible to deflation.

The health effects of asbestos inhalation include asbestosis, mesothelioma (a cancerous tumor of the lung lining or pleural cavity), and lung cancer. Some asbestos fibers penetrate body tissue and remain in the lungs, lung lining, and abdominal cavity. Radiographically visible fibrosis may take as much as 15–20 years to appear following initial exposure.

Interstitial lung disease is best documented in the scientific literature on occupational situations, but cases of nonoccupational asbestosis have been reported in several countries in Europe and around the Mediterranean, including Czechoslovakia, Austria, Bulgaria, Greece, and Turkey.

In central Turkey, inhalation of agricultural soils rich in tremolite (a common fibrous amphibole) and erionite is responsible for an endemic malignant pleural mesothelioma. Incidence of this disease is specific to certain villages surrounded by soils containing one or both of these minerals (29).

In northern Corsica, incidence of pleural plaques (a fibrous thickening of the lining of the lung cavity walls), associated with mesothelioma, has been found in residents with no history of occupational contact with asbestos. A clear regional contrast exists between northeast and northwest regions (separated by a mountain range exceeding 2300 m in altitude). Of more than 1700 subjects examined by radiograph, 3.7% of those born in northeast Corsica (with rocks rich in serpentine, asbestos, and chrysotile) were found to have bilateral pleural plaques,

compared with only 1.2% of those born in the northwest. Residents born close to asbestos outcrops showed an excess of subjects with bilateral plaques (94.6%), compared with only 5.4% of subjects born in unexposed villages (30). The evidence of high levels of chrysotile fibers in the atmosphere of the northeastern region points to a direct link between disease incidence and inhalation.

## CONCLUSIONS

- i) The geologic and meteorological study of dust sources, sinks, transport, and geochemistry is an essential foundation for improved understanding of the extent and magnitude of the potential impacts of natural minerogenic aerosols on human health.
- ii) The pathological effects of prolonged exposure to natural mineral dust have been recognized in a general way since ancient times, but the number of modern studies of pneumoconiosis outside occupation-specific contexts remains small.
- iii) The specific health effects of direct inhalation of high concentrations of fine minerogenic dusts, generated by natural deflation from loose, poorly bound soil surfaces, including those exposed by accelerated erosion of weak geologic formations such as loess, thus remain rather poorly known and relatively little researched.
- iv) The magnitude of the world's population affected by inhalation of fine mineral aerosols can only be estimated at present. It is likely to number millions of people in the middle latitude desert zone especially across Eurasia between the eastern Mediterranean and the Yellow Sea.
- v) Way of life is an important factor in any assessment of the health impact of respirable mineral dust because it directly affects dust generation, resuspension, and inhalation in many of the world's drylands.
- vi) Systematic, transdisciplinary research programs designed to quantify the respiratory health status of people in the same environments, but with contrasting dust exposure potential, and taking full account of other risk factors, including those of anthropogenic origin (occupational conditions, cigarette smoking, life-style, etc.), will be needed to complement any environmental monitoring. Much more detailed characterization of the properties of natural ambient dusts will also be needed to underpin such programs.

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# Global Impacts Of Geogenic Arsenic: A Medical Geology Research Case

## INTRODUCTION

Arsenic (As) is a ubiquitous element, and it is the 20th most abundant element in the Earth's crust. Humans can be exposed to As through the diet or from natural environmental sources, such as contaminated groundwater, soils, or burning coal. Anthropogenic (man-made) sources of exposure to As may include the use of As in medicine (e.g., Fowler's solution or  $\text{AsO}_3$ ), industrial pollution, mining, and the burning of chromate-copper-arsenate-treated wood.

Inorganic As (In-As), found in surface and groundwater sources, is generally composed of pentavalent arsenate ( $\text{As}^{\text{V}}$ ) and/or trivalent arsenite ( $\text{As}^{\text{III}}$ ). Upon ingestion, In-As is metabolized in a 2-step process that involves reduction and oxidative methylation reactions to produce the monomethylarsonic acid ( $\text{MMA}^{\text{V}}$ ) and the dimethylarsenic acid ( $\text{DMA}^{\text{V}}$ ) before it is excreted in the urine. Because these methylated species are easily excreted in the urine (i.e., in most populations exposed to As, total urinary As is composed of approximately 60–80%  $\text{DMA}^{\text{V}}$ , 10–20%  $\text{MMA}^{\text{V}}$ , and 10–20% In-As), they are generally considered to be less toxic than In-As species. Thus, methylation is generally thought as a "detoxification" pathway of As in humans. Inorganic  $\text{As}^{\text{III}}$  forms are generally considered to be much more toxic than the pentavalent methylated forms; however, recent laboratory findings suggested the formation of intermediate methylation species in the form of monomethylarsonous acid ( $\text{MMA}^{\text{III}}$ ) and dimethylarsinic acid ( $\text{DMA}^{\text{III}}$ ) (1), which may be more toxic than arsenite for certain deoxyribonucleic acid-damage end points (2). Accordingly, not only is the measurement of total As required, but, also, quantification of the individual metabolites is necessary to assess the toxicity and health risk of this element.

The health effects of chronic exposure to As are well established in countries with high levels of As in their drinking water; however, such evidence is not readily available in countries with lower levels of environmental As or with drinking water treatment systems. Of more relevance to developed countries, e.g., United States, are the potential health consequences of long-term low-level exposures via drinking water or through occupation, or wood treatments. This paper is aimed at providing an overview of and a brief discussion of the available literature on global distribution of As as a research case on medical geology.

## BACKGROUND AND GLOBAL IMPLICATIONS

Chronic As toxicity from drinking As-contaminated groundwater has recently been reported from many Asian countries (3). Of these, the catastrophic health problems caused by As in the well waters of Bangladesh and West Bengal, India, have been front page stories in mass media and in scientific journals. Although estimates of how many people are at risk vary, there is no question that it runs into the tens of millions in Bangladesh alone, and, in West Bengal, it is suspected that about 6 million people are exposed to As-contaminated drinking water above the  $50 \mu\text{g L}^{-1}$  As level. This situation was called the "greatest mass poisoning in history" (4). What is often not reported is that the tens of millions of people exposed to As in Bangladesh represent only a portion of the people who are at risk

worldwide. Elevated levels of As were reported in water supplies of communities in Argentina, Austria, Brazil, Canada, China, Ghana, Greece, Hungary, Iceland, India, Japan, Korea, Malaysia, Mexico, Inner Mongolia, Nepal, Romania, Taiwan, Vietnam, Zimbabwe, and the United States (see Fig. 1).

Geoscientists are working with public health officials to seek solutions to these problems. By studying the geological and hydrological environment, geoscientists are trying to determine the source rocks from which As is being leached into the groundwater. They are also trying to determine the conditions under which the As is being mobilized. For example, is the As being desorbed and dissolved from iron oxide minerals by anaerobic (oxygen-deficient) groundwater, or is the As derived from the dissolution of As-bearing sulfide minerals, e.g., pyrite, by oxygenated waters? The answers to these questions will allow the public health communities around the world to identify aquifers with similar characteristics and to more accurately determine which populations may be at risk from As exposure.

## GEOLOGICAL SOURCES OF EXPOSURE

As indicated previously, exposure to As may come from both natural and anthropogenic activities, including industrial sources, mining, medicinal sources, food, and beverages. However, exposure to natural geological sources of As, including groundwater, geothermal springs, volcanic sediments, and As-rich coal led to the largest incidence of reportable poisoning cases in different parts of the world (3). For example, As mobilized through coal combustion caused severe health problems in China (5) and Slovakia (6).

In China's Guizhou Province, the situation is exacerbated by the villagers' domestic use of coal. The coal in this region has extraordinarily high concentrations of As (up to  $35\,000 \mu\text{g g}^{-1}$  As). Thousands of people in this region are suffering from severe As poisoning. Those affected exhibit typical symptoms of As poisoning, including hyperpigmentation (flushed appearance, freckles), hyperkeratosis (scaly lesions on the skin, generally concentrated on the hands and feet), Bowen's disease (dark, horny precancerous lesions of the skin (see Fig. 2)). Chili peppers dried over open coal-burning stoves may be a principal route for the As poisoning. Fresh chili peppers have less than  $1 \mu\text{g g}^{-1}$  As. In contrast, chili peppers dried over high-As coal fires in this region can reach up to  $500 \mu\text{g g}^{-1}$  As. Significant amounts of As may also come from other tainted foods, ingestion of dust (samples of Guizhou kitchen dust contained as much as  $3000 \mu\text{g g}^{-1}$  As), and from inhalation of indoor air polluted by As derived from coal combustion. Interesting, in Guizhou Province, the relatively low As content in drinking water did not appear to make it as important a route of exposure as in other parts of the world, e.g., Bangladesh. To understand the form, mobility, and transport of As from these natural geological sources, as well as to develop solutions to these problems, it is of critical importance to emphasize the need to obtain detailed chemical characterization of those natural geological sources where As may be present. In the case of the coal samples from China, detailed chemical and mineralogical characterization demonstrated that much of the As in these Chinese coal samples is bound to the organic

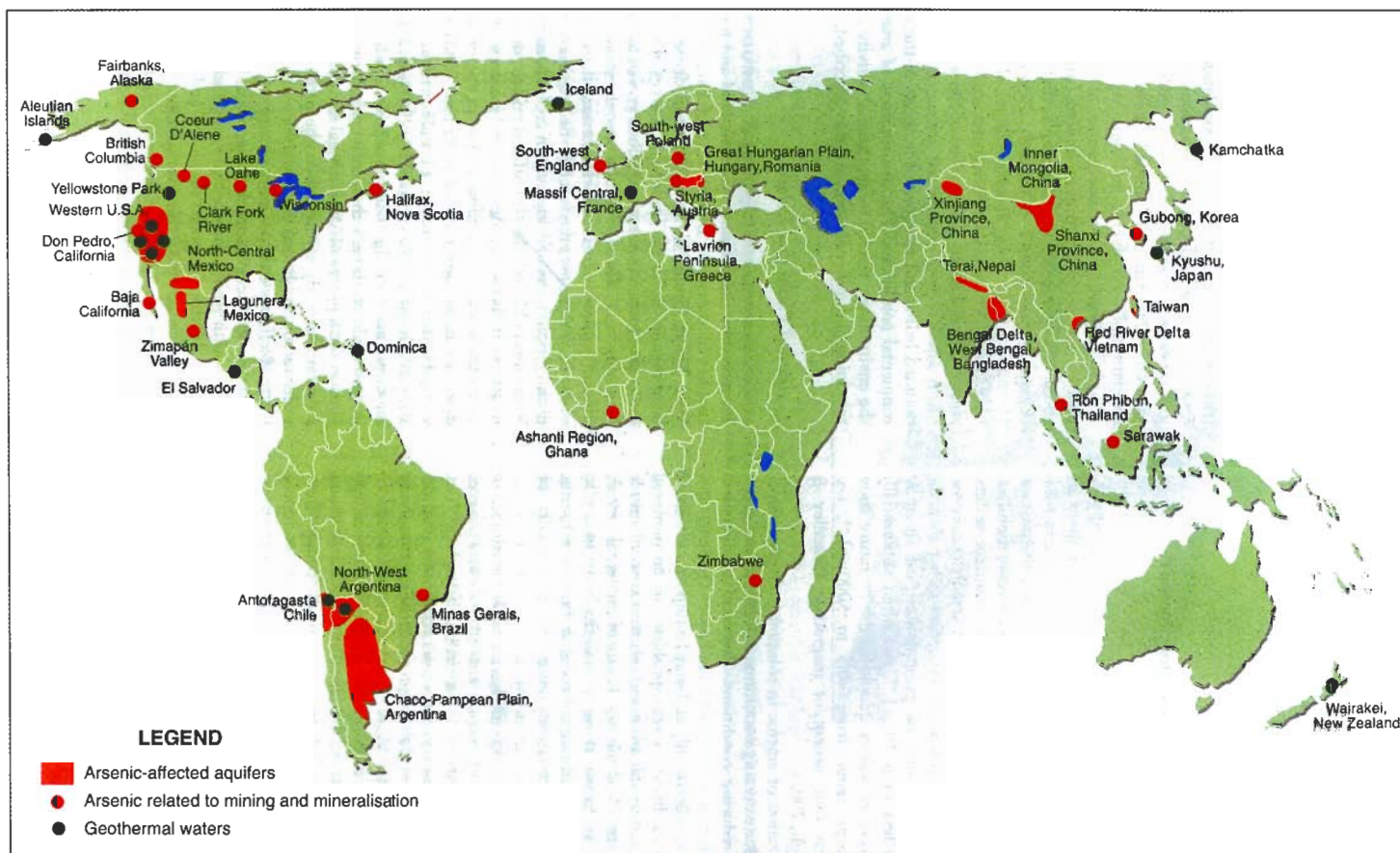


Figure 1. World map illustrating regions with documented arsenic problems in groundwater ( $As > 50 \mu g L^{-1}$ ). Adapted from Ref. 22.

component of these coals and not in pyrite as is typically found worldwide (7). Accordingly, traditional methods of reducing As, e.g., physical removal of heavy minerals, primarily As-bearing pyrite, would not be effective.

In the West Bengal delta, the source of As is also known to be geogenic, but the exposure is through contaminated drinking water. Although the mechanism and the cause by which As may leach from its source has not been fully established, geochemical studies suggested procedures involving oxidation, reduction, and carbon reduction as potential mechanisms for the mobilization of As to the groundwater (3).

In Mexico, chronic As poisoning from contaminated drinking water was reported in 6 areas of the Lagunera region in the central part of north Mexico, with a population of ~200 000 (8). The source of As in this region was suggested to come from volcanic sediment (9). Geogenic As in the soils and groundwater of Zimapan in the Hidalgo area poses an environmental risk for human exposure via the drinking water (10).

In Argentina, elevated levels of As in surface water, shallow wells, and thermal springs have been reported. This natural contamination was associated with volcanic deposits (tertiary-quadernary sediments), together with postvolcanic geysers and a thermal spring. Case studies in the Chaco-Pampean plain report on elevated groundwater As from geogenic sources (11, 12). Groundwater contamination with As was also reported in the Province of Cordoba, Argentina, with As concentrations exceeding  $100 \mu g L^{-1}$  (13).

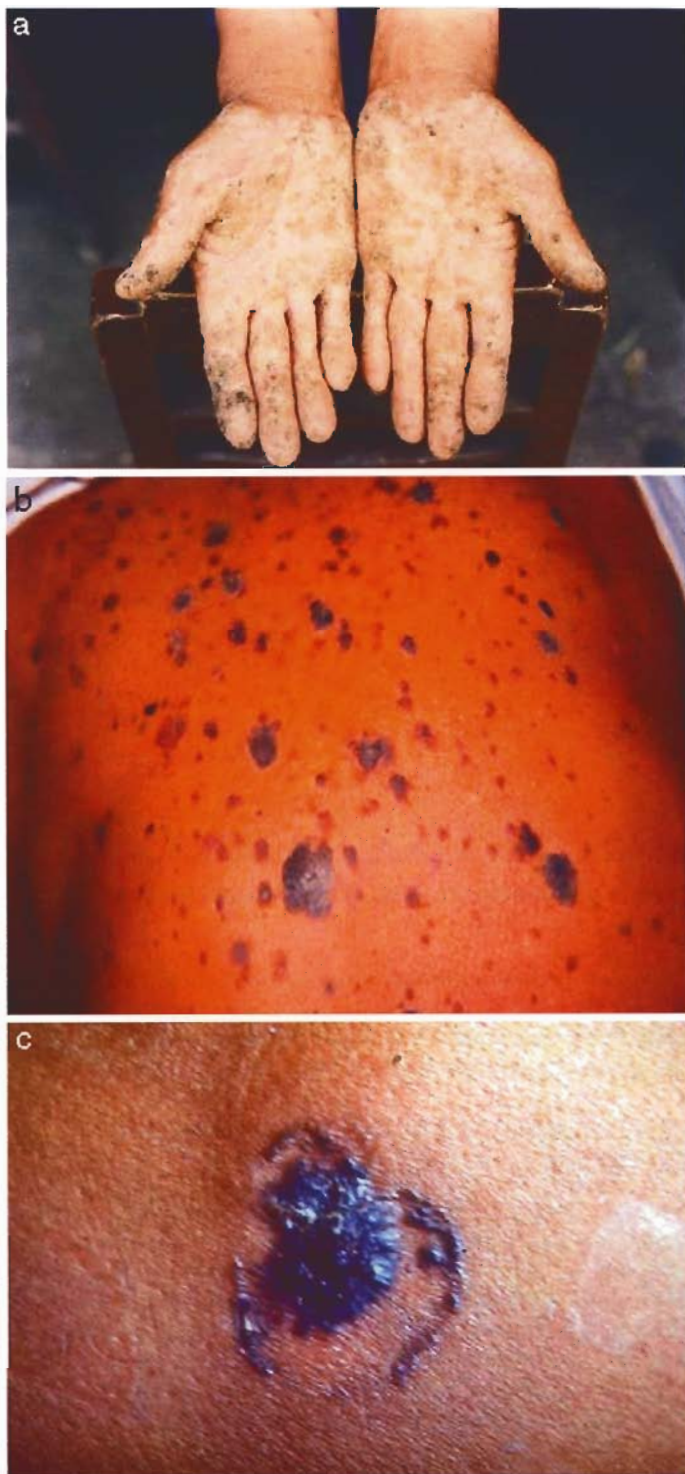
In Antofagasta, Chile, several epidemiological studies document the As-related health problems from years of drinking water with As levels as high as  $800 \mu g L^{-1}$  (14). In this region, tertiary-quadernary sediments, minerals, and soils were suggested as the sources of As (15).

Arsenic exposure through drinking well water in Taiwan was initially recognized in the 1960s, and it was stopped in the late 1970. Pyrite occurring in the black shales underlying geological strata was suggested to be the source of As (16).

## HEALTH IMPACTS FROM CHRONIC ARSENIC EXPOSURE

Inorganic As is well documented as a human carcinogen of the skin and lungs. Significantly high prevalence of skin cancer was observed in all arseniasis-endemic areas around the world, particularly in Asia. Inorganic-As was demonstrated to also affect many other organ systems, including the gastrointestinal, hepatic, cardiovascular, nervous, renal, and hematopoietic systems. Arsenic is a systemic toxicant known to induce cardiovascular diseases; developmental abnormalities; neurologic and neurobehavioral disorders; diabetes mellitus; mental retardation; ischemic heart disease; peripheral polyneuritis and polyneuropathy; peripheral vascular disease and limb gangrene; hypertension; hearing loss; and hematologic, gastrointestinal, renal, and respiratory disorders. The severity of adverse health effects is related to the source of exposure (natural and/or anthropogenic), the chemical form of the element (i.e., speciation), as well as the dose and duration of As exposure, although nutritional status and As methylation capacity may be involved in the determination of individual susceptibility to develop As poisoning.

Perhaps the single most characteristic effect of long-term oral exposure to In-As is a pattern of skin changes. These include a darkening of the skin and the appearance of nodular and diffuse lesions on the palms, soles, and torso (see Fig. 2) (17). Chronic As exposure from oral ingestion and inhalation has been associated with a variety of internal cancers involving the gastrointestinal tract, urinary bladder, lung, liver, and kidney



**Figure 2. Arsenical-induced skin lesions. (a) The palms show multifocal hyperkeratotic lesions. (b) Skin of back with raindrop-like chronic arsenic-induced hyperkeratotic lesions. (c) Arsenic-induced Bowen's disease.**

(18, 19). Research has also pointed to significantly higher standardized mortality rates for cancers of the bladder, kidney, skin, and liver in many areas of As pollution (20).

Early recognition of As exposure and health effects may contribute to timely consideration of the As health risk and preventive measures. Being aware of these health impacts it seems important to communities and individuals relying on groundwater sources for drinking water to monitor the As levels to ensure that supplies are safe (20). Communities with water As levels  $>5 \text{ g L}^{-1}$  should consider a program to regularly monitor diagnostic [e.g., As in urine, nails, hair, and, recently, blood

(21)] and clinical effect markers (e.g., skin lesions) for As in the population. Research efforts, therefore, should focus on environmental and human markers for early recognition of exposure and poisoning, and on risk assessment.

## CONCLUSION

Arsenic contamination through natural (geogenic) and anthropogenic sources is a serious threat to humans all over the world. Natural sources of As exposure may include contaminated groundwater, volcanic sediments, coal, and spring thermal waters. The number of people affected by As is staggering, the problems are life threatening, the scope is global, and the potential for medical geology interventions is enormous. In this manuscript, we provide an overview of the global health impacts from chronic As exposure. There is sufficient evidence from human epidemiological studies in Taiwan, Chile, Argentina, and Bangladesh to conclude that ingestion of As in drinking water poses a hazard of cancer of the lung and the bladder, in addition to cancer of the skin. However, no human studies of sufficient statistical power or scope have examined whether consumption of As in drinking water at the current World Health Organization standard of 10 ppb results in an increased incidence of cancer or noncancer effects. Therefore, research efforts are urgently needed to better understand the health risk assessment from chronic low-exposure levels to As, as well as speciation studies to better define the distribution of As in the natural environment, food, and other sources of exposure.

Medical geology has the objectives of identifying harmful geologic agents; determining exposure relating to deteriorating health conditions; and developing sound principles, strategies, programs, and approaches to eliminate or minimize health risks, with particular focus on the naturally occurring physical and chemical agents in the environment. Interaction and communication should be encouraged between the geoscience and biomedical/public health communities to seek novel solutions to better protect human health from the damaging effects of As exposure.

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# Blackfoot Disease in Taiwan: Its Link with Inorganic Arsenic Exposure from Drinking Water

## INTRODUCTION

Blackfoot disease (BFD) was an endemic peripheral vascular disease confined to the southwestern coast of Taiwan. Typical symptoms and signs of progressive arterial occlusion were mainly found in the lower extremities, but the upper extremities might also be involved in rare cases. Ulceration, gangrene, and spontaneous or surgical amputation were typical results (1, 2). Sporadic cases of BFD occurred as early as in the early 20th century, and peak incidence was noted between 1956 and 1960, with prevalence rates ranging from 6.51 to 18.85 per 1000 population in different villages. The disease could afflict patients in a wide range of ages, from 2 to 87 y, but the mean age of onset was 52 y (1). The sex ratio for men to women was 1.5:1 (1). The etiology of this endemic disease has been extensively sought during the past 50 y. This paper reviews the link between the exposure to arsenic from drinking artesian well water and the development of the disease.

## ARSENIC EXPOSURE AND PREVALENCE OF BLACKFOOT DISEASE

BFD is an endemic disease confined to the southwestern coast of Taiwan. The disease is characterized by progressive narrowing of the peripheral vessels involving mainly the lower extremities. In rare cases, the upper extremities can also be involved (1). Clinical manifestations are characteristic of ischemia involving the lower legs, such as numbness or coldness, intermittent claudication, or absence of peripheral pulsation in the initial stage (1). The afflicted subjects might develop ulceration and gangrene in the involved extremities in a later stage, and spontaneous or surgical amputation was the typical result. Sporadic cases were noted since the early 20th century. However, not much attention had been paid until after the mid-20th century when cumulative case numbers became noticeable. Peak incidence of BFD was found between 1956 and 1960 (2, 3). The concentration of arsenic in the drinking water from the artesian wells in the endemic areas has been found to be high, with the median concentration ranging from 0.70 to 0.93 mg L<sup>-1</sup> (4, 5), in comparison with the shallow well water in other areas of Taiwan, which ranged between nondetectable and 0.30 mg L<sup>-1</sup> with a median of 0.04 mg L<sup>-1</sup> (5). Tseng collected a series of more than 1600 cases and followed the patients for more than 30 y (1). According to his early analyses, a dose-responsive relationship between arsenic concentration in the artesian wells and the prevalence of BFD was found in different age groups of residents in the endemic areas. In villages where the arsenic concentrations in well water were <0.30 mg L<sup>-1</sup>, 0.30–0.59 mg L<sup>-1</sup>, and more than 0.60 mg L<sup>-1</sup>, the prevalence rates of BFD for residents aged 20–39 y were 0.5%, 1.3%, and 1.4%, respectively; for residents aged 40–59 y, 1.1%, 3.2%, and 4.7%, respectively; and for residents aged over 60 y, 2.0%, 3.2%, and 6.1%, respectively (1). This study suggested that the prevalence of BFD increased in proportion to increasing arsenic concentrations of the well water.

## ARSENIC EXPOSURE AND PERIPHERAL VASCULAR DISEASE

Since the early 1990s Tseng et al. carried out a series of studies by using more objective tools such as Doppler ultrasound and laser Doppler flowmetry in combination with exercise test for diagnosis of subclinical defects in arterial flow and microcirculation and by considering the cumulative exposure dosage of arsenic and the potential effect of confounders. Subclinical arterial insufficiency (6) and microcirculatory defects (7) were clearly demonstrated before the development of clinically full-blown BFD in seemingly normal subjects living in the endemic areas after prolonged exposure to the well water containing high arsenic concentrations. A dose-response relationship between indices of long-term arsenic exposure dosage at individual levels and peripheral vascular disease was also clearly demonstrated, which was independent of the confounding effects of lipid profiles and other traditional cardiovascular risk factors (8, 9). The prevalence of peripheral vascular disease for those with a cumulative arsenic exposure of 0, 0.1–19.9, and ≥20 mg L<sup>-1</sup> × y were 4.4, 11.6, and 19.8%, respectively; and the respective odds ratios (95% confidence interval) were 1.00, 2.77 (0.84–9.14), and 4.28 (1.26–14.54) after adjustment for potential confounders (2). The prevalence of peripheral vascular disease for those living in the endemic areas for ≥60 y could be as high as 28.4% and the multivariate-adjusted odds ratio was 10.54 (2.68–41.37), compared with those living in the endemic areas for less than 40 y (2). These later studies fortified the link between arsenic exposure and the development of peripheral vascular disease in the BFD-endemic areas in Taiwan.

In a recent study, Tseng et al. further demonstrated the influence of the interaction between arsenic exposure and urinary arsenic species on the risk of peripheral vascular disease diagnosed by Doppler ultrasound in 479 (220 men and 259 women) adults residing in the BFD areas in Taiwan (10). Arsenic exposure was estimated by cumulative arsenic exposure; and urinary levels of total arsenic, inorganic arsenite and arsenate, monomethylarsonic acid (MMA<sup>V</sup>), and dimethylarsinic acid (DMA<sup>V</sup>) were determined; and primary methylation index (PMI = MMA<sup>V</sup>/urinary inorganic arsenic) and secondary methylation index (SMI = DMA<sup>V</sup>/MMA<sup>V</sup>) were calculated. The association between peripheral vascular disease and urinary arsenic parameters was evaluated considering the interaction with cumulative arsenic exposure and the confounding effects of age, sex, body mass index, total cholesterol, triglycerides, cigarette smoking, and alcohol consumption. The results showed that the risk of peripheral vascular disease increased with a higher cumulative arsenic exposure and a lower capacity to methylate arsenic to DMA<sup>V</sup> after taking into account the potential effect of confounders. The multivariate-adjusted odds ratios for cumulative arsenic exposure of 0, 0.1–15.4, and >15.4 mg L<sup>-1</sup> × y were 1.00, 3.41 (0.74–15.78), and 4.62 (0.96–22.21), respectively (*p* < 0.05, trend test); and for PMI ≤ 1.77 and SMI > 6.93, PMI > 1.77 and SMI > 6.93, PMI ≤ 1.77 and SMI ≤ 6.93, and PMI ≤ 1.77 and SMI ≤ 6.93 were 1.00, 2.93 (0.90–9.52), 2.85 (1.05–7.73), and 3.60 (1.12–11.56), respectively (*p* <

0.05, trend test). It was concluded that individuals with a higher arsenic exposure and a lower capacity to methylate inorganic arsenic to DMA<sup>V</sup> have a higher risk of developing peripheral vascular disease in BFD areas in Taiwan. This is the first study showing an effect of arsenic methylation capacity on the development of arsenic-induced peripheral vascular disease. Therefore, the results of recent studies suggested that susceptibility to peripheral vascular disease is not only related to the exposure dosage of arsenic in the BFD areas. The capacity to metabolize and detoxify inorganic arsenic plays a significant role on the susceptibility and development of peripheral vascular disease in subjects chronically exposed to arsenic. Subjects with a higher capacity to methylate inorganic arsenic to DMA<sup>V</sup> would have a lower risk of developing clinical disease.

## REVERSIBILITY OF INCIDENCE OF BFD AND MORTALITY FROM PERIPHERAL VASCULAR DISEASE

The association between arsenic exposure and BFD is also supported by the observation that patients with BFD had a high co-occurrence of arsenic-related skin lesions such as hyperpigmentation, hyperkeratosis, and skin cancer (11). This co-occurrence of skin lesions and BFD could not be attributed to chance alone, and chronic arsenic exposure is the common cause or underlying factor (11). In a recent study, seemingly normal subjects living in the BFD-endemic areas were also found to have subclinical sensory nerve defects. While comparing the current perception thresholds measured by a Neurometer<sup>®</sup> at the trigeminal, median, and superficial peroneal nerves with frequencies of 5, 250, and 2000 Hz, 85 seemingly normal subjects living in the BFD-endemic areas were noted to have significantly (1.28- to 2.23-fold) higher current perception thresholds than 75 external normal controls without arsenic exposure (12). Since neuropathy is a common feature of arsenic intoxication, the findings of subclinical defects in sensory nerves also give supportive information for the possible link between arsenic exposure and the etiology of BFD.

Another way to demonstrate the link between arsenic exposure and BFD was to use the reversibility criterion in the evaluation of a cause-effect relationship. The different rates of BFD between residents consuming well water and those consuming tap water in the same areas and the dramatic decline of BFD after implementation of tap water supply systems to the endemic villages identifies arsenic from artesian well water as a causative agent of BFD. Tap water supply to the endemic areas was not available before the 1960s, and its coverage remained low until the 1970s. The incidence rates per 100 000 person-years for men and women who consumed artesian well water were 44.3 and 36.5, respectively; and were 2.9 and 3.1 for men and women who used tap water in the same areas (2). Most new cases of BFD after the 1970s occurred in people above 50 y of age in both genders, while BFD might occur in those below 30 y of age before the 1950s (2). By analyzing the mortality attributed to peripheral vascular disease in the BFD-endemic areas for the years 1971–2003, Yang also demonstrated a gradual decrease of mortality from peripheral vascular disease over a period of 25–27 y after the cessation of consumption of the artesian well water (13). The decline of the incidence of BFD and the reversibility of mortality from peripheral vascular disease in the endemic areas after cessation of the use of the artesian well water strongly suggested a link between the high arsenic-containing well water and the development of BFD.

## CONCLUSIONS

Exposure to inorganic arsenic can be associated with a variety of human diseases involving different organs and systems. The

link between BFD and arsenic exposure from drinking water has been demonstrated for nearly 50 y in Taiwan. More recent studies also demonstrated the existence of subclinical defects in the arterial system and microcirculatory flow in seemingly normal subjects living in the BFD-endemic areas with prolonged arsenic exposure. The link between peripheral vascular disease before full-blown BFD and arsenic exposure has fortified the potential risk of atherogenicity associated with arsenic exposure. Actually the atherogenicity of arsenic is systemic and not limited to the lower extremities. Our recent study also demonstrated a link between arsenic exposure and ischemic heart disease (14). Environmental exposure to a variety of chemicals can be causative to cancers (15–20); arsenic is also a carcinogen found in environmental, occupational, and medicinal exposure (21–24). Exposure to arsenic is not only atherogenic, it can also be associated with a higher risk of developing diabetes (25–27) and hypertension (28), both of which can accelerate the atherogenicity of arsenic and clinical development of cardiovascular disease.

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# Radon: Sources, Health Risks, and Hazard Mapping

## INTRODUCTION

There are 3 naturally occurring radon (Rn) isotopes:  $^{219}\text{Rn}$  (actinon),  $^{220}\text{Rn}$  (thoron), and  $^{222}\text{Rn}$ , which is commonly called radon. Radon-222 is a natural radioactive gas produced by the radioactive decay of radium ( $^{226}\text{Ra}$ ), which, in turn, is derived from the radioactive decay of uranium. Uranium is found in small quantities in all soils and rocks, although the amount varies from place to place. Radon-222 or  $^{222}\text{Rn}$  (radon) occurs in the uranium-238 decay series, has a half-life of 3.82 d, and provides about 50% of the total radiation dose to the average person. Radon concentrations (1) in outdoor air are generally low ( $4\text{--}8\text{ Bq m}^{-3}$ ), whereas radon in indoor air ranges from less than  $20\text{ Bq m}^{-3}$ , to about  $110\,000\text{ Bq m}^{-3}$  with a population-weighted world average of  $39\text{ Bq m}^{-3}$ . Country averages range from  $9\text{ Bq m}^{-3}$  in Egypt,  $20\text{ Bq m}^{-3}$  in the UK,  $46\text{ Bq m}^{-3}$  in the US,  $108\text{ Bq m}^{-3}$  in Sweden, and  $140\text{ Bq m}^{-3}$  in the Czech Republic (2). Radon in soil air (the air that occupies the pores in soil) commonly varies from 5 to  $50\text{ Bq L}^{-1}$  but may be  $<1\text{ Bq L}^{-1}$  or more than  $2500\text{ Bq L}^{-1}$ . The amount of radon dissolved in ground water ranges from about 3 to nearly  $80\,000\text{ Bq L}^{-1}$  (3).

This synopsis describes the kinds of rocks and unconsolidated deposits that radon is associated with, how radon moves through the ground and into buildings, the associated health risks, and how to produce radon hazard maps. It is an updated summary of Appleton, J.D. 2005. Radon in air and water. In: *Essentials of Medical Geology: Impacts of the Natural Environment on Public Health*. Selinus, O. (eds). Elsevier, Amsterdam, pp. 227–262.

## GEOLOGICAL ASSOCIATIONS

Relatively high levels of radon emissions are associated with particular types of bedrock and unconsolidated deposits, for example, some granites, uranium-enriched phosphatic rocks, and shales rich in organic materials (3). Uranium concentrations also sometimes occur in limestones, sedimentary ironstones, and permeable sandstones. Rock types that are high radon sources in the US include *i*) uraniumiferous metamorphic rocks and granites, especially fault shear zones in these rocks in the Sierra Nevada, Rocky, and Appalachian mountain ranges; *ii*) marine black shales, especially in a belt from Ohio to Colorado; *iii*) glacial deposits derived from uranium-bearing rock and sediment, especially in the northwestern Midwest, where high radon emanation reflects large surface area and high permeability caused by cracking when dry; *iv*) uranium- and radium-enriched soils derived from carbonate, especially karstic terrain; *v*) uranium-mining residues and mine tailings in western US (e.g., Colorado); and *vi*) phosphate ore close to the surface and in mining waste on the surface, especially in Florida. Releases from coal residues and the burning of natural gas and coal complete the list of major contributors to atmospheric radon in the US (4).

High concentrations of radon in houses and soil gas in the UK are associated with *a*) rocks and weathering products that contain enhanced levels of uranium or radium, and *b*) permeable rocks, unconsolidated overburden, and their weathering products. Granites in southwest England are characterized

by high uranium concentrations, a deep weathering profile, and uranium in a mineral phase that is easily weathered. Although the uranium may be removed during weathering, radium generally remains *in situ* (5). Radon is easily emanated from the weathered rock, and high values of radon have been measured in ground and surface waters ( $110\text{--}740\text{ Bq L}^{-1}$ ) and in soil gas (frequently  $>400\text{ Bq L}^{-1}$ ). There is a clear correspondence between areas where more than 30% of the house radon levels are above the UK Action Level ( $200\text{ Bq m}^{-3}$ ) and the major granite areas (3, 5).

The depositional and diagenetic environment of many black shales leads to enrichment of uranium. For example, some Carboniferous shales in north England contain  $5\text{--}60\text{ mg kg}^{-1}$  uranium. Weathering and secondary enrichment can substantially enhance uranium (U) levels in soils derived from these shales. Fifteen percent to 20% of houses sited on uraniumiferous shales with  $>60\text{ mg kg}^{-1}$  U and high soil-gas radon ( $32\text{ Bq L}^{-1}$ ) are above the UK radon Action Level (6). Sedimentary ironstone formations in the UK, including the Jurassic Northampton Sand Formation and the Marlstone Rock Bed, are slightly uraniumiferous and permeable, so a relatively large proportion of houses underlain by these rocks are affected by high radon concentrations (3). High levels of radon occur in both soil gas and houses underlain by Carboniferous Limestone in the UK, as well as in caves and mines. Ten percent to more than 30% of houses built on the limestones have radon concentrations greater than the UK Action Level (7–9).

Similar associations between high radon and Lower Carboniferous limestones, Namurian uraniumiferous and phosphatic black shales, some granites, and highly permeable fluvio-glacial deposits have also been recorded in Ireland (10).

In the Czech Republic, the highest indoor and soil-gas radon levels are associated with the Variscan granites, granodiorites, syenites, and phonolites of the Bohemian massif. Syenites contain  $12\text{--}20\text{ mg kg}^{-1}$  U, phonolites have  $10\text{--}35\text{ mg kg}^{-1}$  U, and soil-gas radon concentrations range up to more than  $450\text{ Bq L}^{-1}$ . High radon is also associated with Palaeozoic metamorphic and volcanic rocks, and also with uranium mineralization in the Příbram area (11, 12).

In Germany, the highest radon occurs over the granites and Palaeozoic basement rocks. Median soil-gas radon for some granites ranges from  $100\text{ to }200\text{ Bq L}^{-1}$  (13). In contrast, the highest radon potential in Belgium is associated with strongly folded and fractured Cambrian to Lower Devonian bedrocks in which uranium preferentially concentrated in ferric oxyhydroxides in fractures and joints is considered to be the main source of radon (14). In France, some of the highest radon levels occur over peraluminous leucogranites or metagranitoids in a stable Hercynian basement area located in South Brittany (western France). These rocks are derived from uraniumiferous granitoids, with average uranium contents of over  $8\text{ mg kg}^{-1}$  (15). High radon is associated with granite and alum shale in Sweden, Norway, and Belgium (16–18). In India, the soil-gas and indoor radon concentrations are controlled by lithology, structure, and uranium mineralization (19), whereas in Korea, high soil-gas radon is associated with granite gneiss and banded gneiss, and low concentrations occur in soils over shale, limestone, and phyllite schist (20).

The impact of unconsolidated deposits reflects their permeability and composition. In Sweden, fragments and mineral grains of uranium-rich granites, pegmatites, and black alum shales are dispersed in till and glaciofluvial deposits, leading to high radon in soils and dwellings, especially when the glaciofluvial deposits are highly permeable sands and gravels (21). In Norway, high radon is associated with highly permeable fluvioglacial and fluvial deposits derived from all rock types and with moderately permeable unconsolidated sediments (mainly basal till) that contain radium-rich rock fragments (17).

## RELEASE AND MIGRATION OF RADON GAS

Most of the radon atoms formed from the decay of radium remain in the mineral grains. In soils, normally 20%–40 % (in clays up to 70%) of the newly generated radon atoms emanate to the pore space where they are mixed in the gas (soil air) or water that fill the pores. From the pore space, radon can be transported by diffusion or by flow in carrier fluids, such as gas (soil air) or water. The rate of release of radon from rocks and soils is largely controlled by their uranium and radium concentrations, grain size, and by the types of minerals in which the uranium occurs. The most important factors controlling its migration and accumulation in buildings include *i*) the transmission characteristics of the bedrock, including porosity and permeability; *ii*) the nature of the carrier fluids, including carbon dioxide gas, surface water, and groundwater; *iii*) weather; *iv*) soil characteristics, including permeability; *v*) house construction characteristics, and *vi*) life style of house occupants (22).

After uranium and radium concentration, the permeability and the moisture content of rocks and soils are probably the next most significant factors influencing the concentration of radon in soil gas and buildings. The maximum distance that radon can diffuse through water is about 5 cm. Thus, in unsaturated rocks and overburden with high fluid permeability, higher radon values are likely to result from a given concentration of uranium and radium than in less permeable or water-saturated materials. The fracturing of clays, resulting in enhanced permeability, combined with clays' relatively high radium content and its emanation efficiency may also result in higher radon concentrations in dwellings.

Radon containing soil air (or soil gas) is transported along natural pathways, which include planar discontinuities and openings, such as bedding planes, joints, shear zones, and faults, as well as potholes and swallow holes in limestone. Artificial migration pathways underground include mine workings, disused tunnels, and shafts, as well as near-surface installations for electricity, gas, water, sewage, and telecommunications services. For example, higher radon (average 480 Bq m<sup>-3</sup>) was found in houses located ±150 m from the surface projection of a closed uranium mine tunnel in Hungary compared with houses located further away [average 291 Bq m<sup>-3</sup> (23)]. Radon is thought to migrate through fissures that intersect the mine tunnel and run up to the surface.

Out of doors, radon normally disperses in the air, whereas in confined spaces, such as buildings, mines, and caves, it may accumulate. Derived from soils and rocks underlying a building, radon in indoor air is transported into the building with soil gas through holes and cracks in the foundation. Normally radon transport by diffusion is not the cause of enhanced radon concentrations in dwellings, although diffusion may be more important in buildings with crawl spaces or those that lack a protecting concrete slab. Smaller amounts of radon may be released by degassing of domestic radon-containing water into the indoor air or from building materials. Soil gas represents the predominant source of indoor <sup>222</sup>Rn gas. Indoor radon

concentrations are generally about 1000 times lower than radon in the soil underlying the house. Most houses draw less than 1% of their indoor air from the soil, although houses with low indoor air pressures, poorly sealed foundations, and several entry points for soil air may draw as much as 20% of their indoor air from the soil. Consequently, radon levels inside the house may be very high even in situations where the soil air has only moderate amounts of radon.

The design, construction, and ventilation of the home affect indoor radon levels. Radon-containing soil air can be transported into a home through cracks in solid floors and walls below construction level; through gaps in suspended concrete and timber floors and around service pipes; through crawl spaces, cavities in walls, construction joints, and small cracks or pores in hollow-block walls.

Radon decays in a few days, so water in rivers and reservoirs usually contains very little radon. Consequently, homes that use surface water do not have a radon problem from their water. Water processing in large municipal systems aerates the water, which allows radon to escape, and also delays the use of water until most of the remaining radon has decayed. However, in some parts of the US and Sweden, ground water is the main water supply for homes and communities. These small public water works and private domestic wells often have closed systems and short transit times that do not remove radon from the water or permit it to decay. In such situations, radon from the domestic water released during showering and other household activities could add radon to the indoor air. Areas most likely to have problems with radon from domestic water supplies include those with high levels of uranium in the underlying rocks. This association has been observed in the US, the UK, and Sweden (24, 25).

Building materials generally contribute only a very small percentage of the indoor air <sup>222</sup>Rn concentrations. However, in a few areas, concrete, blocks, or wallboard made by using radioactive shale or waste products from uranium mining will make a larger contribution to the indoor radon. (26–28).

## EXPOSURE AND HEALTH RISKS

The average person in the UK receives an annual effective radiation dose of 2.8 millisieverts (29), of which about 85% is from natural sources: cosmic rays, terrestrial gamma-rays, the decay products of <sup>220</sup>Rn and <sup>222</sup>Rn, and the natural radionuclides in the body ingested through food and drink. About 60% of the total natural radiation dose is from radon isotopes (24, 27, 30). On an individual basis, the dose depends upon where one lives, one's life style, and the nature and extent of any medical treatment. Most of the exposures to terrestrial gamma-rays and to <sup>220</sup>Rn and <sup>222</sup>Rn decay products result from living indoors. Most of the radon that is inhaled is exhaled again before it has time to decay and irradiate tissues in the respiratory tract. Radon (<sup>222</sup>Rn), however, decays to form very small solid radioactive particles, including polonium-218, that become attached to natural aerosol and dust particles. These may remain suspended in the air or settle onto surfaces. When these particles are inhaled, they irradiate the bronchial epithelial cells of the lung with alpha particles, and this may increase the risk of developing lung cancer. Apart from lung cancer, there is no epidemiological proof of radon causing any other type of cancer (31, 32).

A large body of epidemiological data has accumulated over several decades relating to studies of the incidence of lung cancer in miners, and risk estimates have been derived from this data (33). A combined analysis of underground-miners epidemiological studies revealed an increase in relative risk from about 2% at a mean exposure of 250 WLM (1 WLM = working

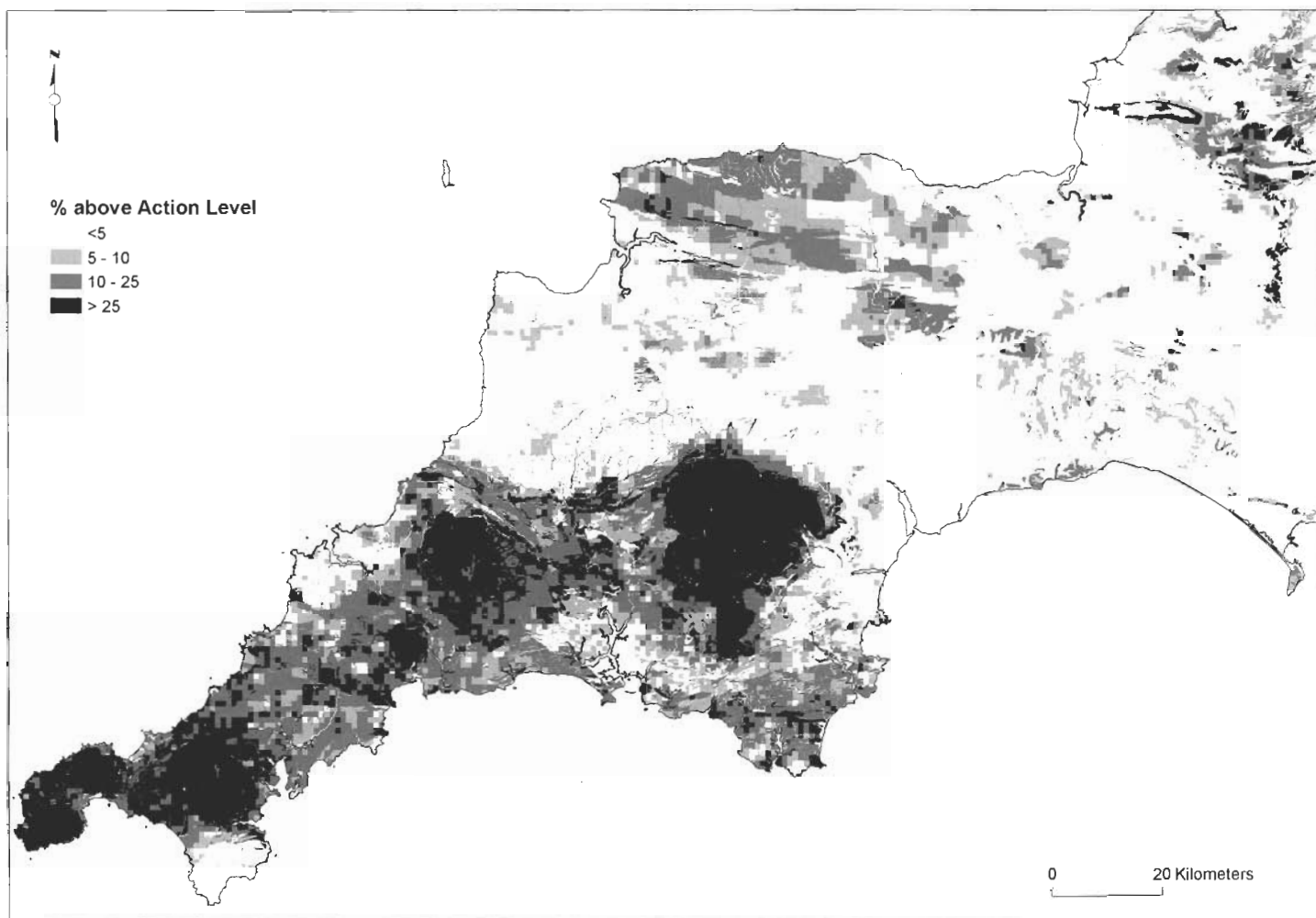


Figure 1. Provisional radon potential map of southwest England based on geology and indoor radon measurements.

level month, equivalent to an average annual exposure of  $144 \text{ Bq m}^{-3} \text{ y}$  to 10% at 2500 WLM (34).

Collaborative analysis of individual data from 13 case-control studies of residential radon and lung cancer in 9 European countries showed that the risk of lung cancer increased by 16% (95% confidence interval, 5%–31%) per  $100 \text{ Bq m}^{-3}$  increase in radon after correction for random uncertainties in measuring radon concentrations (35). The dose-response relation seemed to be linear, with no threshold and remained significant ( $P = 0.04$ ) in analyses limited to individuals from homes with measured radon  $< 200 \text{ Bq m}^{-3}$ . The results suggest that radon is responsible for about 2% of all deaths from cancer in Europe. Systematic analysis of pooled data from 711 North American residential case-control radon studies showed that the odds ratios (OR) for lung cancer increased with residential radon concentration. The estimated OR after exposure to radon at a concentration of  $100 \text{ Bq m}^{-3}$  over a 25-y period was 1.11 (1.00–1.28), which is compatible with the estimate of 1.12 (1.02–1.25), predicted by downward extrapolation of the results from occupational studies of radon-exposed underground miners (36, 37).

The number of lung-cancer cases from residential radon exposure in the US is estimated to be 15 000 to 22 000, which is 10%–15% of lung cancer deaths. Radon causes 11% of lung cancer deaths among smokers (most of whom die of smoking) but 23% of persons who never smoked. Darby et al. (38) demonstrated that over 80% of the radon related deaths in the UK occur at ages of less than 75 and over 80% in smokers or ex-smokers. About 90% of radon induced deaths in the UK probably occur in response to exposure to radon concentrations

below the currently recommended action level of  $200 \text{ Bq m}^{-3}$  of which 57.3% (1304 deaths) can be attributed to residential radon below  $50 \text{ Bq m}^{-3}$  (38). The total number of deaths from lung cancer in the UK is about 34 000, most of them directly from smoking. The cumulative absolute risk of lung cancer by age 75 years, at a residential radon concentration of  $100 \text{ Bq m}^{-3}$  is approximately 12% for smokers and 0.5% for nonsmokers. The US Environmental Protection Agency estimates that radon in drinking water causes about 168 cancer deaths per year, 89% from lung cancer caused by breathing radon released from water, and 11% from stomach cancer caused by drinking radon-containing water. In general, radon released from tap water and inhaled will present a greater risk than radon ingested through drinking water (30).

## RADON HAZARD MAPPING

Accurate mapping of radon-prone areas helps to ensure that the health of occupants of new and existing dwellings and workplaces is adequately protected. Radon potential maps can be used *i*) to assess whether radon protective measures may be required in new buildings; *ii*) for the cost-effective targeting of radon monitoring in existing dwellings and workplaces; and *iii*) to provide a radon assessment for home buyers and sellers. It is important, however, to realize that radon levels often vary widely between adjacent buildings, because of differences in the radon potential of the underlying ground, as well as differences in construction style and use. Whereas, a radon potential map can indicate the relative radon risk for a building in a particular locality, it cannot predict the radon risk for an individual

building. In the UK, radon potential maps generally indicate the probability that new or existing houses will exceed a radon reference level, which in the UK is called the Action Level ( $200 \text{ Bq m}^{-3}$ ) (3, 30). In other countries, geological radon potential maps predict the average indoor radon concentration (US) or give a more qualitative indication of radon risk (Germany and the Czech Republic).

Two main procedures have been used for mapping radon-prone areas. The first is geological radon potential mapping in which each geological feature is assigned to a radon potential class based on the interpretation of one or more of the following types of data: *i*) radon concentrations in dwellings (indoor radon); *ii*) concentration, mineralogical occurrence, and chemical state of uranium and radium in the ground (radiometric and geochemical data); *iii*) rock and soil permeability and moisture content; *iv*) concentration of radon in soil gas, and *v*) building architecture (construction characteristics). The second uses radon measurements in existing dwellings to map the variation of radon potential between administrative or postal districts, or grid squares, or within geological polygons (39, 40).

Uranium and radium concentrations in surface rocks and soils are useful indicators of the potential for radon emissions from the ground. Uranium can be estimated by gamma spectrometry either in the laboratory or by ground, vehicle, or airborne surveys. The close correlation between airborne and ground radiometric measurements and indoor radon concentrations has been demonstrated in Virginia and New Jersey in the US, Nova Scotia in Canada, and also in parts of England (39, 41) although areas with high permeability have significantly higher indoor radon levels than would be otherwise expected from the  $e^{226}\text{Ra}$  concentrations, reflecting an enhanced radon flux from permeable ground (9, 42).

Sweden was the first country to make use of airborne gamma-ray spectrometry data to produce maps of radon potential. Radon potential is estimated and mapped on the basis of available data including *i*) geology; *ii*) airborne radiometric surveys (covering 65% of Sweden); *iii*) results from radiometric surveys of the ground; *iv*) results from radon surveys in buildings; *v*) results from earlier geotechnical investigations (e.g., permeability and ground water level); *vi*) field surveys, including gamma spectrometry; *vii*) orientation soil-gas radon measurements. Åkerblom (43) established a simple 3-fold radon risk classification based on geology, permeability, and soil-gas radon. A similar classification was used for the radon risk map of Estonia (44).

Radon risk mapping of the Czech Republic at a scale of 1:500 000 is based upon a number of data sets for airborne radiometry, geology, pedology, hydrogeology, ground radiometry, and soil-gas radon. Radon risk maps at the 1:50 000 scale are used for the identification of dwellings exceeding the guidance level to an accuracy of 70%–80% (11), although the maps are not recommended for the prediction of the requirement for radon protective measures in new buildings for which soil-gas radon site assessments are required (45).

It has been demonstrated in a number of countries, including Canada, Czech Republic, Germany, the UK, the US, and Sweden that soil-gas radon measurements combined with an assessment of ground permeability can be used to map geological radon potential in the absence of sufficient indoor radon measurements. Ten to 15 soil-gas radon measurements are generally required to characterize a site or geological unit. The Swedish National Board of Housing, Building, and Planning has adopted a ground classification based on geology, permeability, and soil-gas radon measurement (21). Similar procedures are used in Finland, Germany, and the Czech Republic (45). However, soil-gas radon data may be difficult to interpret because of the effects of large diurnal and seasonal

variations in soil-gas radon close to the ground surface, as well as variations in soil-gas radon on a scale of a few meters.

Because the purpose of maps of radon-prone areas is to indicate radon levels in buildings, maps based on actual measurements of radon in buildings are generally preferable to those based on other data. Procedures for monitoring and surveys of radon in dwellings are described in (46) and (47). Requirements for mapping radon-prone areas by using indoor radon data are similar, whether the maps are made on the basis of grid squares or geological units. These requirements include *i*) accurate radon measurements made by using a reliable and consistent protocol; *ii*) centralized data holdings; *iii*) sufficient data evenly spread; and *iv*) automatic conversion of addresses to geographical co-ordinates. It appears that Great Britain is the only country that currently meets all of these requirements for large areas. In countries where lesser quality or quantity of indoor radon data is available, there is greater reliance on proxy data for radon potential mapping (e.g., Czech Republic, Germany, Sweden, and the US).

Radon measurements in existing dwellings have been used to map the radon potential of countries, administrative districts, or grid squares, without taking into consideration the geological controls on radon in dwellings. Because the factors that influence radon concentrations in buildings are largely independent and multiplicative, the distribution of radon concentrations is usually lognormal, so lognormal modeling was used to produce accurate estimates of the proportion of homes above a reference level in the UK (48, 49). Radon potential mapping that used indoor radon measurements have been carried out in other European countries, including Ireland, Luxembourg, and France (50).

Radon maps based on indoor radon data grouped by geological unit have the capacity to accurately estimate the percentage of dwellings affected together, with the spatial detail and precision conferred by the geological map data (51). Combining the grid square and geological mapping methods gives more accurate maps than either method can provide separately [(40); Fig. 1].

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29. The absorbed dose (measured in Gy or rad) is the energy absorbed by a unit mass of tissue, whereas the dose equivalent takes account of the relative potential for damage to living tissue of the different types of radiation. The dose equivalent is the absorbed dose multiplied by a “quality factor,” which is 1 for beta and gamma rays and 20 for alpha particles. This is because alpha particles deposit their energy much more densely. In addition, alpha particles transfer all their energy in short distances so that a relatively small volume of tissue receives a high dose of radiation. The commonly used unit for dose equivalent is the sievert (1Sv = 1000 millisieverts; 1000 mSv). The dose equivalent indicates the potential risk of harm to particular tissues by different radiations, irrespective of their type or energy.
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# Selenium Deficiency and Endemic Heart Failure in China: A Case Study of Biogeochemistry for Human Health

## A PECULIAR DISEASE

In 1937, a terrible disease of heart failure was reported in some rural areas in Heilongjiang, a far northeastern province of China. Women and children were its primary victims. The disease frequently occurred without warning and led to the death of a large number of people. The major symptom of the disease was myocardial necrosis, which led to acute hypoxia, vomiting, and finally death in several hours. Preliminary investigations were conducted in the late 1930s and 1940s but biotic infecting agents could not be identified. The peculiar disease was then named after the county, Keshan, where the first cases of death from the disease were reported. Since then, Keshan disease was found in another 12 provinces across China between the 1940s–60s. About eight million people lived in the affected areas in the country during that period of time, and thousands of people died of Keshan disease every year. The disease was so severe that a special government office was established to coordinate the nationwide efforts against the disease in the 1950s.

In the 1950s and 60s, large-scale epidemiological investigations were launched in the provinces affected by Keshan disease, including Heilongjiang, Jilin, Liaoning, Hebei, Shandong, Henan, Inner Mongolia, Shanxi, Shaanxi, Gansu, Sichuan, Yunnan, and Tibet.

A variety of biotic or abiotic factors, such as indoor carbon monoxides, nitrite in drinking water, parasites, fungi or bacteria in the local diet, etc., were considered during the investigations. The campaigns did not prove any of the factors related to the incidence of Keshan disease with convincing evidence. However, the nationwide investigations demonstrated that Keshan disease occurred within a geographic belt stretching from the northeast to the southwest of China. In some places, the affected and unaffected areas had clear boundaries. It was not uncommon to see two adjacent villages differing in disease status substantially and constantly for decades. Through the field investigations, the possibility that Keshan disease was an infectious one was excluded. The striking spatial distribution of Keshan disease implied that there could be some geographic or geological factors causing the disease. In fact, the local villagers whose families had lived in the affected areas for generations insisted that the disease was caused by the local “soil and water.” A number of medical researchers started looking in a new direction, the geochemical environment. In 1966, Dr. Haijiang Cai, one of the pioneer medical researchers studying Keshan disease in China, declared “We must team up with the geologists who are interested in the medical issues.”

## THE WUYUR RIVER WATERSHED PROTOTYPE

In the winter of 1967, a group of eight young scientists from the Institute of Geochemistry, Chinese Academy of Sciences, were organized to respond to the call of the medical researchers. Realizing that the major challenge for the Keshan disease study was how to explain the peculiar spatial distribution of the disease, the new team oriented their focus on the geochemical patterns of the areas affected by Keshan disease. To implement

their research strategy, the team selected Keshan County in Heilongjiang Province, the origin of Keshan disease, as their first study area. By teaming up with the local medical doctors, this group conducted a thorough field survey by literally walking across the entire county in 1968. They visited almost all the villages in the county, obtaining information on the incidence of Keshan disease as well as the local environmental conditions. Soil and drinking water samples were collected from each of the villages for chemical analysis. The investigation resulted in a map of multiyear cumulative deaths from Keshan disease, with the chemical composition of the drinking water and soils at the village level described for the county. The map demonstrated an interesting pattern of Keshan disease in its geographic distribution in the county. The villages heavily affected by Keshan disease were mostly located in the central part of the county with hilly terrain; in contrast, the villages located along the river valleys along the northern or southern edge of the county had few cases reported during the previous decades. Field investigations indicated the topographic and soil conditions in the central part of the county were favorable for leaching, a geochemical process leading to a loss of dissolved salts or elements from the soils. The observation was supported by the results from the chemical analysis of the soil and water samples. The mineral contents in the drinking water samples collected from the affected villages were significantly lower than those from the unaffected villages. A hypothesis emerged from the investigations that Keshan disease could be caused by a deficit of a chemical or chemicals that are essential for human health and exist in soluble or leachable forms in the soils (1).

To test the hypothesis, the field investigation was expanded from Keshan County to the Wuyur River watershed in 1969–1970, within which Keshan County was located. Wuyur River is an interior river with a length of about 300 km. The river begins in Beian County in the foothills of the Xiao-Xinganling Mountains; flows to the southwest across Kedong, Keshan, Yian, Fuyu, and Lindian counties; and finally ends in the low-lying plains in Durbat County (Fig. 1). As an interior river, the Wuyur River doesn't have a coastal outlet; this implied to the researchers that the chemical elements could be transported only within the watershed. If some elements were lost in the soils of the upper stream, they should accumulate in the soils downstream. The Wuyur River watershed provided an ideal domain to test the hypothesis of the relationship between Keshan disease and geochemical leaching. If the areas affected by Keshan disease were characterized with losses of certain soluble elements, it would be very interesting to find out the incidence of Keshan disease in the areas where these elements were deposited downstream.

To complement the investigation of the Wuyur River watershed, the research team was enhanced by involving more medical researchers from the Harbin Medical University, the Institutes of Endemic Diseases of Heilongjiang, and the Institute of Labor and Food Health in the Chinese Academy of Medical Sciences. During the coupled epidemiological and geochemical survey, historical incidence data for Keshan disease were collected and verified at the commune (a cluster of villages)

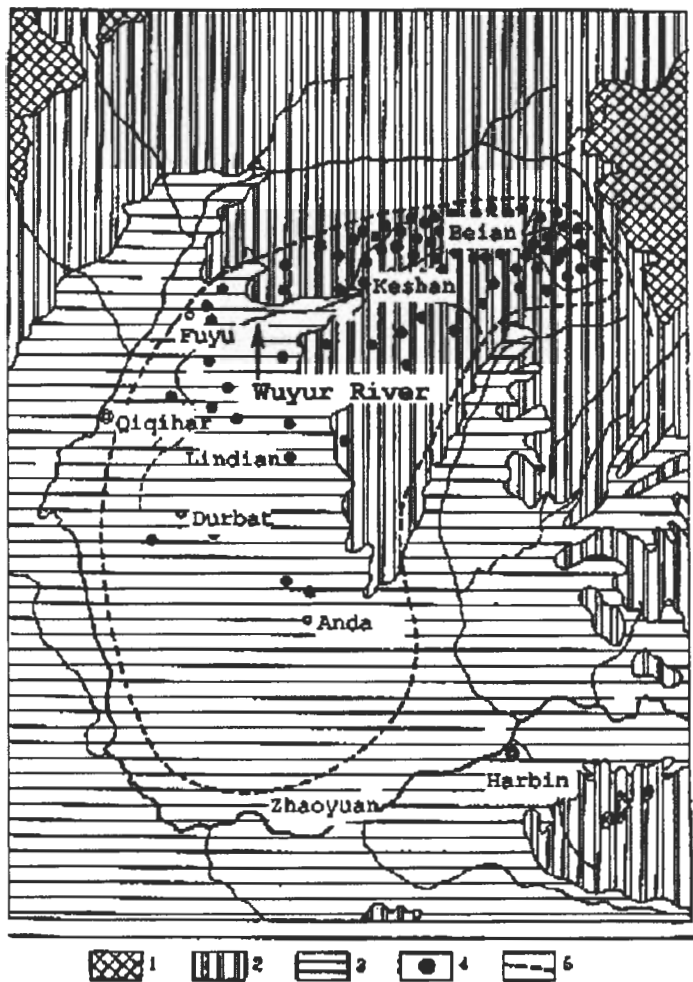


Figure 1. The spatial distribution of Keshan disease is closely related to the geographic conditions in the watershed of the Wuyur River. (Legends: 1. Xiao-Xinganling Mountain, 2. Hilly terrain, 3. Plains, 4. Keshan disease-affected communes, 5. Boundary of Wuyur River watershed) (3).

scale for the entire watershed; meanwhile soil and water samples were collected and analyzed for potassium, sodium, calcium, magnesium, chloride, sulfate, carbonate, bicarbonate, nitrate, nitrite, fluoride, and some trace elements. Results from the survey clearly indicated that the incidence of Keshan disease gradually decreased downstream in the Wuyur River basin (Figure 1); meanwhile the contents of most of the cations and anions in the drinking water increased downstream. For example, in the upstream counties, such as Keshan, Beian, Dedu, and Fuyu, dozens of villagers had died of Keshan disease every year during the previous 15 y. In contrast, in the downstream counties, such as Durbat, Zhaodong, Zhaoyuan, and Anda, no deaths from Keshan disease had been reported during the previous decades. In drinking water, the total mineral contents ranged between 350–680 mg L<sup>-1</sup> for Keshan and Fuyu counties and 750–950 mg L<sup>-1</sup> for Durbat and Zhaoyuan (1, 2). The 2-y watershed investigation confirmed the relationship between Keshan disease and the geochemical environment.

#### ESTABLISHMENT OF A BIOGEOCHEMICAL MODEL

The peculiar distribution of Keshan disease had long been a mystery puzzling the researchers. For example, in Heilongjiang, Keshan disease was reported in dozens of counties, which spread across the entire province without any clear pattern (Fig. 2). Could the hypothesis emerging from the Wuyur River investigation be used to explain the spatial distribution of

Keshan disease in the province? The Wuyur River survey indicated that there were four main environmental factors, namely, climate, topography, vegetation and soil texture, controlling the leaching intensity of the soluble cations or anions in the soils. For example, the upstream areas (e.g., Keshan, Fuyu, etc.) of the Wuyur River watershed were characterized by relatively high precipitation with hilly topography that led to high leaching rates. In contrast, the downstream areas such as Durbat or Zhaoyuan had flat land with low precipitation and high evaporation rates that led to the accumulation of the soluble salts in the soils. In fact, soil salinization was observed in a broad area downstream where Keshan disease had never been reported during the previous 200 y. If Keshan disease was induced by deficiency of certain chemical elements, the correlation of the disease with the environmental factors, which controlled the element leaching intensity, should be identified based on their spatial patterns at the provincial scale. A mathematical model was established to quantify the leaching intensity driven by the four environmental factors (i.e., climate, topography, vegetation, and soil) for the entire Heilongjiang Province. At first, each of the environmental factors was divided into several grades based on its impact on the leaching process. For example, climate was divided into nine grades based on the precipitation/evaporation ratio. Areas with higher precipitation/evaporation rates had a stronger leaching effect, so they were assigned a higher grade number. The same principle was applied to topography, vegetation type and soil texture to produce their grades. Since the grades of all four environmental factors were defined based on the same principle, i.e., their impact on leaching, the grade numbers for the four factors could be summed up to produce a single number to represent the collective effect of the factors on leaching intensity. This single number was called the leaching index (LI). A database was constructed to hold the information on climate, topography, vegetation, and soil for Heilongjiang. The entire Heilongjiang Province was divided into about 1000 grid cells. By overlapping the gridded map with the maps of climate, topography, vegetation, and soil, the researchers obtained the specific climate, topography, vegetation, and soil conditions for each of the grid cells for the entire Heilongjiang Province. A LI value was calculated for each cell based on the specific climate, topography, vegetation, and soil grades in the

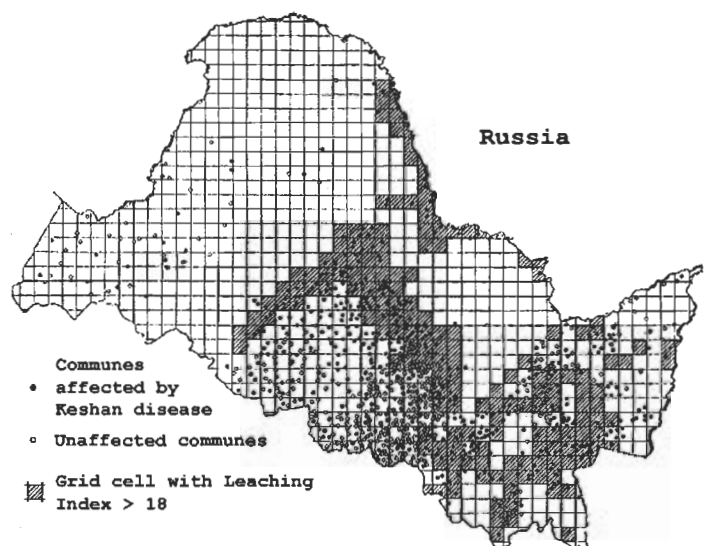


Figure 2. The grid cells with the modeled leaching index (LI) values higher than 18 covered most of the communes affected by Keshan disease in Heilongjiang Province. The spatial coincidence between Keshan disease and LI values indicated that Keshan disease could be related to deficiency of some chemical elements, which were lost from the soils through leaching (3).

cell. The calculations across the 1000 grid cells resulted in a map of leaching intensity (LI) for Heilongjiang Province. On this map, the LI values provided a semiquantitative expression indicating the leaching intensity of the soluble elements across the entire domain.

The LI map was validated against a multiyear observational dataset from 19 local hydrological stations across the province. Observed leaching intensity was calculated for each subhydrological unit based on the unit area and the measured fluxes of minerals (i.e., potassium, sodium, calcium, magnesium, chloride, sulfate, carbonate, bicarbonate, nitrate and nitrite). Meanwhile, a mean LI value for each subhydrological unit was calculated by averaging the modeled LI values for the grid cells included in the subhydrological unit. When the observed leaching fluxes and modeled LI were compared, the two factors demonstrated a significant correlation (3).

To link the LI map with Keshan disease, a threshold value of LI, 18, was selected arbitrarily. By highlighting the grid cells with LI values higher than 18, an irregular pattern was outlined on the map. The pattern was amazingly consistent with the pattern of Keshan disease (Fig. 2) (3).

The success in reproducing the spatial distribution of Keshan disease in Heilongjiang was regarded by medical researchers as a breakthrough for understanding the endemic nature of Keshan disease (4). The biogeochemical modeling practice enhanced the hypothesis of deficiency of essential elements for Keshan disease and then attracted more research focusing on the geochemical causes.

## FOCUSING IN ON SELENIUM

During the field investigations in Heilongjiang Province in 1968–1970, the interdisciplinary team visited several horse farms. It was found that all the horse farms located in the areas affected by Keshan disease suffered from an animal disease, known as white muscle disease. At that time, white muscle disease had been recognized as a myopathy of livestock due to deficiency of a trace element, selenium (Se), and supplements of Se to the livestock effectively prevented the disease (5, 6). Given the understanding that soil Se mainly existed in the forms of selenate or selenite, two highly soluble salts, and hence could be easily leached from the soils, water samples were collected from the affected and unaffected villages in Keshan County for chemical analysis. The results indicated that Se contents in the samples from the affected areas were lower than those from the unaffected areas ( $<0.2$  vs.  $>0.5 \mu\text{g L}^{-1}$ ) (7). Based on the preliminary observations that *i*) Keshan disease mainly occurred in the areas with strong leaching effect; *ii*) Se could be leached from soils easily; and *iii*) white muscle disease existed with Keshan disease in the affected areas, Se deficiency emerged as the most likely cause of Keshan disease. When this idea was presented in a workshop held in Shangzhi County in Heilongjiang in 1971, Se received great attention, especially from a group of nutritionists from the Chinese Academy of Medical Sciences. Prevention experiments were almost immediately launched to test the hypothesis in the same year.

The spatial relationship between Keshan disease and livestock white muscle disease was observed not only in Heilongjiang but also in Shaanxi, Gansu, Sichuan, and other provinces during the same time period. In the 1970s and even the early 1980s, a wide range of geoscientists and medical researchers were involved in quantifying Se contents in soil, water, food, human hair, urine, and blood samples collected from the areas affected by Keshan disease and adjacent areas. Results from the analytical tests indicated that the spatial distribution of Se was basically consistent with that of Keshan disease. Along the belt

from the northeast to the southwest of China where Keshan disease was reported, Se contents in the soils ranged from 0.03 to 0.10  $\text{mg kg}^{-1}$ . In contrast, in the southeastern or northwestern part of China where there was no Keshan disease reported, the soil Se contents were usually higher than 0.12  $\text{mg kg}^{-1}$  (8). The Se contents in food were also significantly different between the affected and unaffected areas. For example, Se contents were  $0.005 \pm 0.003$ ,  $0.007 \pm 0.003$ , and  $0.010 \pm 0.008 \text{ mg kg}^{-1}$  in samples of corn, rice and soybeans, respectively, from the affected areas, and  $0.036 \pm 0.056$ ,  $0.035 \pm 0.027$ , and  $0.069 \pm 0.076 \text{ mg kg}^{-1}$  in corn, rice, and soybeans, respectively, from the unaffected areas in China (9).

Preventive experiments supplementing Se in the diet were conducted in most of the provinces affected by Keshan disease in the 1970s and 1980s. Selenium-containing tablets or supplements were adopted to directly increase Se doses in the diets, or Se fertilizer was applied to the soil to increase the Se content in the food (10). The decade-long preventative campaign finally eliminated Keshan disease nationwide in China.

## DISCUSSION

Keshan disease was a special phenomenon occurring under specific natural and social conditions in China. Until very recently, most Chinese farmers were bound to their local land, which was almost the only source of food and drinking water to the local residents. If there was anything abnormal with the geochemical conditions in the land, e.g., deficiency of essential elements or accumulation of toxic chemicals, the villagers had little chance to escape (11). As a human health problem, Keshan disease had complex features influenced by seasonality, gender, age, etc. Deficiency of Se was an important, but not the only, factor affecting the incidence of Keshan disease. Now we have learned that Se is an essential element in glutathione peroxidase (GSH-Px), which plays an important role in antioxidant defense (12). In human diets, the range of Se content between deficiency ( $<40 \mu\text{g a day}$ ) and toxicity ( $>400 \mu\text{g a day}$ ) is narrow. A small dosage of supplement can protect people from the disease. Along with the drastic changes in the entire socioeconomic structure of China in the 1980s and 1990s, the contemporary transportation systems of food reaching even the very remote corners of the country have fundamentally eliminated the local deficiency of Se in the diet.

Keshan disease is becoming a historic term. However, reviewing the processes of the Chinese researchers during the Keshan disease studies can teach us something. That is that interdisciplinary approaches, such as medical geology, could play a crucial role in human health-related environmental problems (13). The human beings on this planet are faced by a series of unprecedented changes in the environment at local, regional, and global scales. Every species is in a hurry to adjust itself for adaptation. New problems related to human health are arising due to pollution, climate change, or biological or chemical weapons. The concepts and methodologies developed in geosciences, specifically in biogeochemistry, could be directly applied to a wide range of environmental issues by linking spatial or temporal patterns displayed by these problems to biogeochemistry, which determines the abundance, coupling, and cycling of various chemical compounds or elements in the environment that control people's health and life (14, 15). I hope the story of Keshan disease reported in this paper will draw more young scientists to interdisciplinary studies.

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# Selenium Geochemistry and Health

## INTRODUCTION

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, Se has one of the narrowest ranges between dietary deficiency ( $<40 \mu\text{g d}^{-1}$ ) and toxic levels ( $>400 \mu\text{g d}^{-1}$ ) (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 Se in the soils on which we grow the crops and animals that form the human food chain. The Se 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 Se in humans, understanding the biogeochemical controls on the distribution and mobility of environmental Se is key to the assessment of Se-related health risks.

## Selenium in the Environment

The element was first identified in 1817 by the Swedish chemist Jons Jakob Berzelius; its chemical behaviour resembles that of sulphur and it exists in the  $2^-$ ,  $0$ ,  $4^+$ , and  $6^+$  oxidation states. As a result of this complex chemistry, Se is found in all natural materials on Earth including rocks, soils, waters, air, and plant and animal tissues. Se is widely used in a number of industries, as a pigment in glass and ceramic manufacture, as the light-sensitive photoconductor layer in photocopiers, as a catalyst in organic synthesis, as an antioxidant in inks and oils, and as an antifungal agent in pharmaceuticals (2–4).

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 Se as rocks are the primary source of the element in the terrestrial system (5, 6).

**Selenium in Rocks.** In general, Se concentrations in rocks are low. Sedimentary rocks contain more of the element than igneous rocks, but even so, levels in most limestones and sandstones rarely exceed  $0.1 \text{ mg kg}^{-1}$ . Se is often associated with the clay fraction in sediments and is found in greater concentrations in shales ( $0.06 \text{ mg kg}^{-1}$ ) than limestones or sandstones. Very high concentrations ( $\leq 300 \text{ mg kg}^{-1}$ ) have also been reported in some phosphatic rocks. Coals and other organic-rich deposits can be enriched in Se relative to other rock types, typically ranging from 1 to  $20 \text{ mg kg}^{-1}$ , although values of over  $600 \text{ mg kg}^{-1}$  have been reported in some black shales. Se is often found as a minor component of sulphide mineral deposits whereas elemental  $\text{Se}^0$  is only occasionally reported (5–10). Therefore, the distribution of Se in the geological environment is highly variable reflecting the variability of different rock types.

**Selenium in Soils.** In most circumstances there is a very strong correlation between the concentration of Se in geological parent materials and the soils derived from them. The Se content of most soils is very low  $0.01$  to  $2 \text{ mg kg}^{-1}$  (world mean  $0.4 \text{ mg kg}^{-1}$ ) but high concentrations of up to  $1200 \text{ mg kg}^{-1}$  have been reported in some seleniferous areas (5, 6, 8, 11).

Although the underlying geology is the primary control on Se in soils, the mobility and uptake into plants and animals, known as the bioavailability, is determined by a number of

biophysio-chemical parameters. These include the pH and redox conditions, the chemical form or speciation of Se, 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 Se as even soils that contain adequate total Se concentrations can result in Se deficiency if the element is not in a readily bioavailable form. Under most natural redox conditions, selenite ( $\text{Se}^{4+}$ ) and selenate ( $\text{Se}^{6+}$ ) are the predominant inorganic phases. Selenite is adsorbed onto soil particle surfaces with greater affinity than selenate, especially at low pH in the presence of iron oxide and organic matter. Hence, selenite is less bioavailable than selenate. In contrast, selenate is generally soluble, mobile and readily available for plant uptake in neutral and alkaline soils. Elemental Se ( $\text{Se}^0$ ) and selenides ( $\text{Se}^{2-}$ ) tend to exist in reducing, acid, and organic-rich environments only and are largely unavailable to plants and animals (5, 8, 11).

Therefore, in any study of the Se status of soil, consideration of the likely bioavailability is important. Several different techniques are available to assess bioavailability, but one of the most widely accepted indicators is the water-extractable Se content, which is generally  $<0.1 \text{ mg kg}^{-1}$  in most soils (7, 8).

**Selenium in Plants.** Although there is little evidence that Se is essential for vegetation growth, it is incorporated into the plant structure. Se concentrations in plants generally reflect the levels of Se in the environment. However, an important factor that may determine whether or not Se-related health problems manifest in animals and humans is the very wide-ranging ability of different plant species to accumulate Se. Rosenfield and Beath (12) were the first to classify plants on the basis of Se uptake when grown on seleniferous soils. Se-accumulator plants can absorb  $>1000 \text{ mg kg}^{-1}$  of the element, whereas non-accumulators, such as grain crops and grasses, usually contain  $<50 \text{ mg kg}^{-1}$ . Some species of the plant genera *Astragalus*, *Haplopappus*, and *Stanleya* are characteristic of seleniferous semi-arid environments, however, other species in these genera are nonaccumulators (4, 5, 8).

**Selenium in Water.** Se forms a very minor component of most natural waters and rarely exceeds  $10 \mu\text{g L}^{-1}$ . Typically ranges are  $<0.1$  to  $100 \mu\text{g L}^{-1}$  with most concentrations below  $3 \mu\text{g L}^{-1}$  (4, 8). In general, groundwaters contain higher Se concentrations than surface waters due to greater contact times for rock-water interactions (10). Groundwaters containing  $1000 \mu\text{g L}^{-1}$  Se have been noted in Montana, US and up to  $275 \mu\text{g L}^{-1}$  in China (8, 13). The World Health Organization currently set a maximum admissible concentration of  $10 \mu\text{g L}^{-1}$  for Se in drinking water. However, the most important exposure route to Se for animals and humans is the food we eat, as concentrations are orders of magnitude greater than in water and air in most circumstances (1).

## Selenium Toxicity and Health

Se toxicity problems related to natural exposure occur rarely in animals and humans, but have been reported in Australia, Brazil, China, Ireland, Israel, Russia, South Africa, and the US.

**Selenium Toxicity in Animals.** Se toxicity problems have been recorded for hundreds of years although the cause was unknown. A hoof disease in livestock was reported in Colombia



**Figure 1. Hair loss as a result of Se toxicity, Enshi District, China. Photo: Prof. Mao Dajun ©BGS, NERC.**

in 1560 and in South Dakota, US in the mid-19<sup>th</sup> century where the symptoms were termed alkali disease. In 1931, this disease was identified as Se toxicosis (selenosis).

The relationships between geology, soil Se, uptake into plants, and health outcomes in animals were first examined in detail during the 1930s by Moxon (14). Soils capable of producing Se-rich vegetation toxic to livestock were reported over black shales of the Great Plains of the US. Subsequent studies into Se-deficiency diseases in animals lead to one of the first maps of the Se status of soils, vegetation and animals and the establishment of the classic Great Plain seleniferous soil types (15).

In natural conditions, acute Se intoxication, which results in death, is uncommon as animals are not normally exposed to high-Se forage. Chronic Se intoxication after ingestion of plants containing 5 to 40 mg kg<sup>-1</sup> over weeks or months is more common and leads to two conditions known as alkali disease and blind staggers in grazing animals. Alkali disease is characterized by dullness, lack of vitality, emaciation, rough coat, sloughing of the hooves, erosion of the joints and bones, anaemia, lameness, liver cirrhosis, and reduced reproductive performance. Blind staggers results in impaired vision and

blindness, anorexia, weakened legs, paralyzed tongue, laboured respiration, abdominal pain, emaciation, and death (1, 4, 16).

Although much of the work into Se toxicity has focused on agricultural species, selenosis has also been reported in wild aquatic species and birds. One of the best-known examples affected birds at the Kesterson Reservoir, California, US. Se concentrations in agricultural drainage water entering the Kesterson Reservoir area between 1983 and 1985 were 300 mg L<sup>-1</sup> as a result of contact with seleniferous soils developed over marine black shales in the catchment area. In this arid alkaline environment, 98% of the Se was in the most readily bioavailable selenate form. Studies revealed that 22% of bird eggs contained dead or deformed embryos as a result of Se toxicity. It is estimated that at least 1000 birds died at Kesterson in the period 1983–1985 as a result of consuming plants and fish with 12 to 120 times the normal amount of Se (8).

*Selenium Toxicity in Humans.* Overt Se toxicity in humans is far less widespread than Se deficiency. Nine cases of acute Se 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 2-y old boy (4).

In China, an outbreak of endemic human selenosis was reported in Enshi District, Hubei Province during the 1960s. The condition was associated with consumption of high-Se crops grown on soils derived from coal containing up to 6000 mg kg<sup>-1</sup> Se. Enshi is interesting because elsewhere in the District, Se-deficiency diseases [Keshan Disease (KD)] occur within 20 km of the seleniferous region entirely as a result of geology. Jurassic sandstones, which contain low concentrations of Se, underlie the northwest of the District and KD is present in this area. Studies revealed Se concentrations in soil, food, and human samples from areas underlain by coal up to 1000 times higher than in samples from the selenium-deficient areas. In the seleniferous region, between 1923 and 1988, 477 cases of human selenosis were reported. Hair and nail loss were the prime symptoms of the disease (Fig. 1), but disorders of the nervous system, skin, and paralysis also occurred (7, 17, 18). Further investigations carried out by Fordyce et al. (13) showed that in the seleniferous villages, concentrations of Se 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 strata and use of coal ash to condition the soil. Villagers were advised to avoid cultivating fields underlain by the coal and were counselled against using ash as a soil conditioner. No incidences of Se toxicity have been reported in recent years and it is no longer considered a public health problem in China.

### Selenium Deficiency and Health

Se was identified as an essential trace element during pioneering work into Se-responsive diseases in animals in the late 1950s and early 1960s. In terms of biological function, approximately 25 essential selenoproteins have now been identified in microbes, animals, and humans, many of which are involved in redox reactions acting as components of the catalytic cycle (1, 19). In complex interactions with vitamin E and fatty acids, Se plays an essential biological role as part of the enzyme glutathione peroxidase (GSH-Px), which protects tissues against oxidative damage. As such, Se has been linked to enzyme activation, immune system function, pancreatic function, DNA repair, and detoxification (1, 4, 16, 20). Se has been identified as a component of the cytochrome P<sub>450</sub> system in humans and animals; however, the exact biological role of this seleno-protein has yet to be established (1, 4, 21). Important developments in recent years have shown that Se is beneficial to thyroid hormone metabolism. There are three seleno-enzymes, which

exert a major influence on cellular differentiation, growth, and development (22). Se is also important in reproduction, it aids the biosynthesis of testosterone. Morphological deformities, immotility, and reduced fertility have been reported in sperm in Se-deficient experimental animals (1, 4, 19).

**Selenium Deficiency in Animals.** Due to the complementary role of Se and Vitamin E, practically all Se deficiency diseases in animals are concordant with vitamin E deficiency. Se is necessary for growth and fertility and clinical signs of deficiency include reduced appetite, growth, production and reproductive fertility, unthriftiness, and muscle weakness (1, 4, 16, 23). These disorders are generally described as white muscle disease.

Indeed, Se deficiency in animals is very common around the globe affecting much of South America, North America, Africa, Europe, Asia, Australia, and New Zealand. Many western countries now adopt Se supplementation programs in agriculture, but these are often not available in South America, Africa, and Asia and livestock productivity is significantly impaired by Se deficiency in these regions (1, 4, 16, 23).

**Selenium Deficiency in Humans.** In humans, no clear-cut pathological condition resulting from Se deficiency alone has been identified; however, the element has been implicated in a number of diseases (1).

**Keshan Disease (KD):** Keshan Disease is an endemic cardiomyopathy (heart disease) that occurs in China. Outbreaks have been reported in a broad belt stretching from Heilongjiang in the northeast to Yunnan in the southwest that transcends topography, soil types, climatic zones, and population types. 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 to 3000 deaths each year (17).

Although the disease occurred in a broad belt across China, investigators noticed that WMD in animals occurred in the same areas and further studies demonstrated that soils and crops were low in Se and affected populations were characterized by poor Se status indicated by hair contents of  $<0.12 \text{ mg kg}^{-1}$  (17, 24). On the basis of these findings, large-scale mineral supplementation was carried out. During the four years of investigation, 21 cases of the disease and 3 deaths occurred in the Se-supplemented group whereas 107 cases and 53 deaths occurred in the control group.

Although the disease proved to be Se-responsive, the exact biological function of the element in the pathogenesis was less clear and seasonal variations in disease prevalence suggested a viral connection. Recent work by Beck (25) has shown that a normally-benign strain of coxsackie B3 (CVB3/0) alters and becomes virulent in either Se-deficient or vitamin E-deficient mice. This work demonstrates not only the importance of Se deficiency in immuno-suppression of the host, but in the toxicity of the viral pathogen as well. As with many environmental conditions, KD is likely to be multifactorial, but even if Se deficiency is not the main cause of the disease, it is clearly an important factor.

As a result of widespread Se supplementation programs and economic and communication improvements in China, the incidence of the disease has dropped to such a low level in recent years that it is no longer considered a public health problem.

As an example of the need to understand the bioavailability of environmental Se, Johnson et al. (26) examined soil, staple crop (wheat and oats), water and human hair Se levels in the KD affected Zhangjiakou region of China. Hair, grain, and water Se concentrations showed an inverse relationship with disease prevalence. As expected, the highest Se contents were reported in villages with lowest prevalence of the disease. However, soil total Se contents showed the opposite relationship and were highest in the villages with greatest disease prevalence. Further examinations into the soil geochemistry demonstrated

that KD-village soils were black or dark brown with a high organic matter content and low pH; hence, Se was not readily bioavailable as it was held in organic matter in the soil. Although these soils contained adequate total Se contents, levels of water-soluble Se were deficient. On this basis, conditioning treatments to raise the soil pH thus increasing the bioavailability of Se or foliar application of Se fertilizer to crops to avoid Se adsorption in the soils were recommended as remediation strategies to increase the levels of Se in local food stuffs.

**Kashin-Beck Disease (KBD):** Kashin-Beck Disease, an endemic osteoarthropathy causing deformity of the affected joints, occurs in Siberia, China, North Korea, and possibly parts of Africa (1, 16, 17). In China, the pattern of disease incidence is concordant with KD in the north of the country, but the links with Se-deficient environments are less clear (17). However, children and nursing mothers were supplemented with 0.5 to 2.0 mg sodium selenite per wk for a period of 6 y and as a result, the disease prevalence dropped from 42 to 4% in children aged 3 to 10 y (17). Other factors have been implicated in the pathogenesis of KBD including mycotoxins and humic substances in drinking water, and it is likely that KBD is multifactorial and occurs as a consequence of oxidative damage to cartilage and bone cells when associated with decreased antioxidant defense.

**Iodine Deficiency Disorders (IDD):** The recent establishment of the role of seleno-enzymes in thyroid function means that Se deficiency is now being examined in relation to the IDD goitre and cretinism. Many areas around the world where IDD are prevalent are deficient in Se, including China, Sri Lanka, India, Africa, and South America (1, 4). Concordant Se and iodine deficiency are thought to account for the high incidence of cretinism in Central Africa, Zaire, and Burundi in particular (27) and Se deficiency has been demonstrated in populations suffering IDD in Sri Lanka (28). However, these links require further investigation to determine the role of Se in these diseases.

**Cancer:** Following studies that revealed an inverse relationship between Se in crops and human blood *versus* cancer incidence in the US and Canada (29), the potential anticarcinogenic effect of Se has generated a great deal of interest in medical science. Many studies to examine the links between Se and cancer have been carried out; however, to date, the results are equivocal. There is some evidence to suggest that Se is protective against cancer due to its antioxidant properties; however, other studies have shown that Se may promote cancer. Studies have demonstrated low levels of Se in the blood of patients suffering gastrointestinal cancer, prostate cancer, or non-Hodgkinson's lymphoma, but there is some evidence to suggest that Se increases the risks of pancreatic and skin cancer (1, 4, 7, 21, 30, 31). A recent study by Appleton et al. (32) found no relationship between Se deficiency and oesophageal cancer in Cixian, China.

Finland provides an interesting case because the government was so concerned about the low level of Se intake in the Finnish diet that in 1984, a national program was initiated to increase the Se content of foodstuffs by adding sodium selenate fertilizers to crops. Mean daily intakes rose from  $45 \mu\text{g d}^{-1}$  in 1980 to 110 to  $120 \mu\text{g d}^{-1}$  between 1987–1990 and  $90 \mu\text{g d}^{-1}$  in 1992. 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, but researchers question whether it is valid to make such intersocietal assessments without a control group for comparison (33).

## Future Issues

In recent years, concern is growing in Europe over declining Se intakes. Europe traditionally imported large quantities of wheat



from North America, which contained high Se contents as it was grown over the black shales of the Prairies, but since the advent of the European Union, most cereals are now more locally derived and as a consequence, daily intakes of Se have been falling. In the UK, for example, marked declines are evident even over a 4-y period from intakes of  $43 \mu\text{g d}^{-1}$  in 1991 to 29 to  $39 \mu\text{g d}^{-1}$  in 1995, which are well below the recommended daily intakes of 55 to  $75 \mu\text{g d}^{-1}$  (19). It is also recently that work has shown better health outcomes in HIV-AIDS patients given Se supplements (34). Indeed, the evidence of viral mutageny under Se-deficiency established by Beck (25) 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 Se-deficient environments of Central and Southern Africa where the disease has reached epidemic proportions. Similarly scientists are currently investigating the role of Se-deficiency in the mutageny of the influenza virus and avian flu (35), the implication being that the more recent virulent strains have emerged in Se-deficient environments and that Se supplementation can protect birds against the virus (36). Looking to the future, understanding the biogeochemical controls on the distribution and mobility of environmental Se is key to the assessment of Se-related health risks. Although overt clinical symptoms of Se toxicity and deficiency are rarely reported, the possible subclinical effects are at present poorly understood and should not be underestimated as medical science continues to uncover new essential functions for this biologically important element.

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# Health Effects of Toxic Organic Substances from Coal: Toward “Panendemic” Nephropathy

## INTRODUCTION

Coal contains myriad organic compounds, some known to be toxic and others that are potentially toxic. Toxic organic compounds found in coal of particular interest include: *i*) condensed aromatic structures (e.g., polycyclic aromatic hydrocarbons), which can act as mutagens, cancer promoters, and endocrine disrupters; *ii*) aromatic amines, which have probable nephrotoxic activity; and *iii*) heterocyclic compounds, which may be carcinogenic and nephrotoxic. Toxic organic compounds can be leached from coal into water supplies, and long-term human exposure to these compounds may lead to disease occurrence, including cancer and renal disease. Despite these potential hazards, little is known about the impact and toxicity of organic substances derived from coal in water supplies. One example of a disease hypothesized to be linked to coal-derived toxic organic compounds in water supplies is Balkan endemic nephropathy (BEN).

In this paper, we summarize results from our studies linking BEN to the leaching of toxic organic compounds from low rank (lignite) Pliocene coal deposits into water supplies (well and spring water) of the rural villages where the disease occurs. We also introduce the idea of panendemic nephropathy (PEN) for BEN-like diseases that are linked to coal-derived toxic organic compounds in water supplies, but that occur outside the Balkans. Preliminary results supporting the PEN hypothesis are presented, with results from proposed PEN areas in Wyoming (WY) and Louisiana (LA). Results of toxicological studies of the effects of organic compounds isolated from water supplies in BEN and PEN areas on human cell cultures are also discussed. China, India, Turkey, and Portugal represent other areas where BEN-like diseases may occur, as a result of the presence of extensive low rank coal deposits and rural populations using untreated water in contact with coal in these nations.

## BALKAN ENDEMIC NEPHROPATHY

Balkan endemic nephropathy (BEN) is a kidney disease of unknown origin, geographically confined to rural villages located along tributaries of the lower Danube River in Bosnia, Bulgaria, Croatia, Romania, and Serbia (1, 2). Villages affected by BEN occur in clusters, and the location of BEN clusters has not changed greatly since the disease was first described in the 1950s (3). Cases of BEN are still being diagnosed (4), and estimates are that 25 000 people currently have BEN (5).

Balkan endemic nephropathy is a tubular interstitial nephropathy leading to end-stage renal failure, with dialysis the typical therapeutic approach. Clinically, BEN most closely resembles analgesic nephropathy. At least 40% of patients diagnosed with BEN also develop renal/pelvic cancer (RPC). Renal/pelvic cancer is rare in the general population, and its high rate of occurrence with BEN is a significant feature of the disease, possibly linked to etiology (6, 7).

Perhaps the biggest challenge in the study of BEN is understanding its etiology (2). Many of the features of BEN suggest an environmental link (1, 2), but genetic factors may

also be important (8, 9). Balkan endemic nephropathy etiology has been studied by researchers from a variety of disciplines, and many factors (microorganisms, metals, radioactivity, trace element imbalances in soil, chromosomal aberrations, mycotoxins, plant toxins, etc.) have been proposed as etiological agents for BEN (1, 2). Despite these efforts, the etiology of BEN is still unknown (1, 10).

## PLIOCENE LIGNITE AND BEN ETIOLOGY

Studies by the US Geological Survey in the early 1990s revealed an apparent close association between BEN endemic areas and the occurrence of Pliocene lignite coal deposits in the former Yugoslavia (11, 12). The link between BEN and Pliocene lignite deposits has more recently been documented in Romania (13, 14). There is also evidence of new BEN areas in Kosovo and in eastern Serbia near the Bulgarian border that are associated with Pliocene lignite deposits. Several hyperendemic BEN villages in Serbia are located directly on top of the extensive Kolubara Pliocene lignite. There are no known Pliocene lignite deposits associated with the small BEN area near Vratza, Bulgaria, but there may be small, undocumented coal deposits, or possibly coaly sediments or shales present.

The observation that BEN areas are in close proximity to Pliocene lignite deposits led to the hypothesis (Pliocene lignite hypothesis) that these coal deposits may be linked to the etiology of BEN. Many wells from BEN villages were observed to have brownish-colored water, suggesting the presence of organic matter (15). It is hypothesized that organic compounds from Pliocene lignite located in the hills surrounding BEN villages are leached into groundwater and transported to water supplies (wells or springs) located in the villages below. People who use the well/spring water are then exposed to the coal-derived toxic organic compounds. The relatively low concentrations of toxic organic compounds present (individual compounds typically  $<1 \mu\text{g L}^{-1}$ , and various compound classes  $10\text{--}100 \mu\text{g L}^{-1}$ ) would favor slow development of the disease over 10 to 30 y or more. The frequent association of BEN with RPC may indicate that the coal-derived toxic organic compounds may elicit both nephrotoxic and carcinogenic effects in susceptible individuals (16, 17).

## GEOCHEMICAL STUDIES TESTING THE PLIOCENE LIGNITE HYPOTHESIS

The first test of the Pliocene lignite hypothesis of BEN etiology involved the examination of water from BEN villages and control sites. If the hypothesis is valid, then the chemistry of water supplies in BEN villages must be different from control sites in the quantity and/or composition of the organic compounds present.

Sampling trips were conducted at least twice yearly (spring and summer) from 2000 to 2006 to collect water samples from BEN areas and control sites. Targeted BEN areas included: *i*) the Drobeta Turnu Severin area in southwestern Romania; *ii*)

the Resita area in western Romania; *iii*) the area west of Nis, Serbia; *iv*) the Kolubara area south of Belgrade, Serbia; and *v*) the Vratza area of northwestern Bulgaria (17, 18). Several types of control sites were examined: *i*) villages near BEN areas, but with no incidence of BEN ever reported, *ii*) municipal water supplies from cities or towns near BEN areas, and *iii*) water from rural villages well outside of the BEN areas. Both well and spring water samples were collected from BEN and control villages. Details on sampling sites and sampling protocols for water collection are provided elsewhere (13, 14, 17, 18).

Initial work focused on solvent-extractable organic compounds present in water samples. Water samples were liquid/liquid extracted with dichloromethane and organic compounds in the extracts analyzed by gas chromatography-mass spectrometry (GC-MS), (13, 14, 17, 18). Results clearly demonstrated that well and spring water samples from BEN villages had greater numbers and concentrations of dichloromethane-extractable organic compounds compared with control sites. Organic compound classes identified in the water from BEN villages included biphenyls, aromatic amines, terpenes, and N-, S-, and O-containing heterocyclic compounds. These compounds were not observed in water from control sites. All of these compound classes are present in low rank coal, and many compounds in these classes are known or suspected of being nephrotoxic or carcinogenic. Seasonal variation in the number and concentrations of organic compounds present in water samples from the BEN villages was also observed, with greater amounts present during the higher rainfall spring season. These results are consistent with the Pliocene lignite hypothesis for BEN.

In addition to examining dichloromethane-extractable organic compounds in water supplies from BEN villages and control sites, we also examined high molecular weight (HMW) organic matter in these water supplies beginning in 2004. High molecular weight organic matter was isolated from water supplies using tangential flow ultrafiltration (TFU), with a 7500 Da nominal molecular weight cutoff membrane cell. The TFU unit operates somewhat like an artificial kidney, continuously concentrating the higher molecular weight organic material and allowing lower molecular weight substances to pass through with the water. In initial work using TFU, 10–30 L of well/spring water was concentrated to 120 ml. Results of TFU experiments showed that wells/springs from BEN villages produced highly colored, organic matter-rich TFU concentrates, while the same volume of water from wells/springs at control sites produced only slightly colored, organic matter-poor TFU concentrates. Thus, there appears to be a much larger amount of HMW organic matter in wells/springs from BEN villages than in water supplies from control sites. This result also supports the Pliocene lignite hypothesis for BEN. The chemical composition of the HMW organic matter in well/spring water from BEN villages is currently under investigation, and it is not known whether any of the material can cause kidney nephropathy or RPC. To address the issue of toxicity, the TFU concentrates isolated from BEN and control sites were used in toxicology studies on human cell cultures, as described later.

Analysis of inorganic substances (metals, anions, nutrients, etc.) in water samples from BEN and control sites was also conducted. Earlier studies found no evidence for involvement of inorganic substances in water supplies in the etiology of BEN (1, 2). Our results concur with these previous studies. We found concentrations of most inorganic substances in water supplies well below US Environmental Protection Agency criteria for drinking water, and no significant differences between concentrations in water supplies from BEN and control sites were observed (17). Only nitrate concentrations (up to 225 mg L<sup>-1</sup>) exceeded drinking water standards, but nitrate concentrations

were equally high at BEN and control sites. Nitrate, therefore, cannot account for the characteristic geographic restriction of BEN. Other workers have also observed ubiquitous high nitrate concentrations in water from rural villages in the Balkans (19), probably from the use of manure and other fertilizers in agriculture. Nitrate could be a cofactor in the etiology of BEN, but because of its ubiquitous occurrence in both BEN and control villages it is unlikely to be the primary etiological factor.

## THE PLIOCENE LIGNITES IN BEN AREAS

Studies of the organic and inorganic geochemistry of the Pliocene lignites from BEN areas were carried out to determine whether these coals had characteristics consistent with the Pliocene lignite hypothesis. Laboratory leaching of Pliocene lignites by aqueous solution was conducted to examine the amount and nature of organic compounds extracted from these coals. Fresh coal samples were collected from several coal mines in the BEN areas of Romania and Serbia for these studies. Coal samples from non-BEN areas of these countries were also collected for comparison.

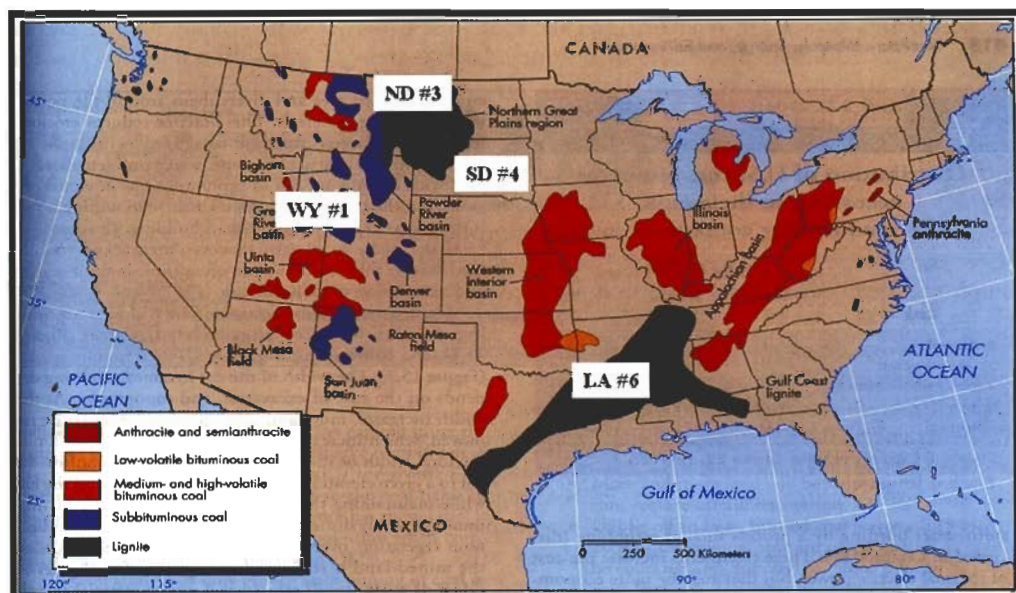
Results show that Pliocene lignites from the BEN areas are less thermally altered than most other lignites but have no unusually high concentrations of inorganic elements (16). Solid-state <sup>13</sup>C nuclear magnetic resonance spectra of BEN area Pliocene lignites show the presence of abundant methoxyl and phenolic functionality, and even the presence of residual cellulose, indicators of a low degree of thermal alteration (20, 21). Elemental organic analysis indicated a high degree of heteroatom (N, O, S) content compared with other lignites (16). These structural features of the Pliocene lignites favor aqueous solubility through hydrogen bonding of organic compounds in the immature coal structure with water.

Laboratory leaching experiments were conducted on the BEN area Pliocene lignites, and other coal samples of comparable and higher rank, using water (extraction at room temperature and 80°C) and a polar solvent (methanol). In these experiments, BEN area Pliocene lignites exhibited the highest yield of extractable organic compounds. Compounds identified in the leachates included many of the compounds identified in water supplies from BEN villages, including cycloalkanes/alkenes, steranic structures, monoaromatic and polyaromatic terpanes, polycyclic aromatic hydrocarbons, aromatic amines, and N-, S-, and O-containing heterocyclic compounds. Many of these compounds have attached oxygen-based functional groups (hydroxy-, phenol-, keto-, methoxy-), and some of them contain heterocyclic nitrogen or amino groups, structural features that could make them nephrotoxic and carcinogenic. Very few of these compounds are encountered in leachates of lignite and higher rank coal from non-BEN areas (17).

## PANENDEMIC NEPHROPATHY (PEN)

The hypothesis linking low rank coal (Pliocene lignites) to BEN is supported by both field and laboratory tests conducted to date. The hypothesis accounts for many of the important features of BEN, including its characteristic geographic distribution, its occurrence only in rural villages (untreated water supply), and its long incubation period (low levels of toxic contaminants). Since low rank coal is found worldwide, however, this hypothesis raises the question of whether diseases similar to BEN might exist outside of the Balkans. We use the term PEN to refer to BEN-like diseases occurring outside the traditional BEN area. Characteristic features of PEN would include high incidence of unexplained kidney disease (including end-stage renal disease and RPC) in a population using untreated water, and water supplies hydrologically connected to low rank coal deposits,

Figure 1. Coal map of the United States showing states with the highest incidence and number of deaths from renal/pelvic cancers (similar to the uroepithelial cancers associated with BEN). All of these states have large rural populations that use well water, and extensive low rank coal deposits (similar to the Pliocene lignites linked to BEN).



Statistics from the National Institutes of Health, USA (22) show that Wyoming (WY), North and South Dakota (ND, SD), and Louisiana (LA) rank among the top 10 states in the United States in incidence and deaths from RPC. Interestingly, all of these states have extensive low rank coal deposits (Fig. 1), and large rural populations using well water. In semi-arid WY, ND, and SD, coal seams are often viewed as good aquifers for water supply. In LA, the highest rates of RPC are in the northwestern part of the state, corresponding to the zone where the lignite deposits are found. A high incidence of RPC is a characteristic feature of BEN, as mentioned earlier. Our emphasis on RPC rather than kidney disease reflects the greater difficulty in separating BEN-like nephropathy from other types of nephropathy in the statistics.

Water supply wells from northwestern LA and from the Powder River Basin (PRB), WY, and coproduced water from coalbed natural gas wells in the PRB were examined for the presence of coal-derived toxic organic compounds. The coproduced water, although not used as a water supply by people, is in direct contact with coal seams, providing information on what types of organic compounds may be leached from coal under natural conditions. Dichloromethane-extractable, and HMW organics (TFU isolation) were examined using the sampling and analytical methods described earlier for the BEN work. Produced water from the PRB contained abundant dichloromethane-extractable and TFU organic matter. Compounds identified in the PRB produced water included polycyclic aromatic hydrocarbons, aromatic amines, and heterocyclic compounds, similar to compounds observed in water extracts of coal, and from BEN area water supplies. Similar results were observed for water supply wells in coal aquifers in the PRB (23). In northwestern LA, water supply wells in the coal area with high rates of RPC had higher numbers and concentrations of organic compounds compared with control sites, and a statistically significant association between the incidence of RPC and the number of different organic compounds in well water and their concentration was determined (24, 25). These results support the concept of PEN.

## TOXICOLOGY STUDIES: BEN AND PEN

Toxicology studies were conducted to further test and validate the hypothesis linking toxic coal-derived organic compounds in drinking water supplies to BEN and PEN. Toxicology studies conducted to date have been limited to *in vitro* experiments

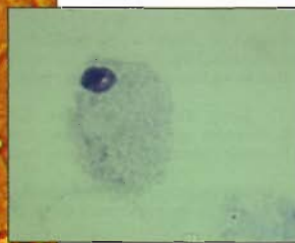
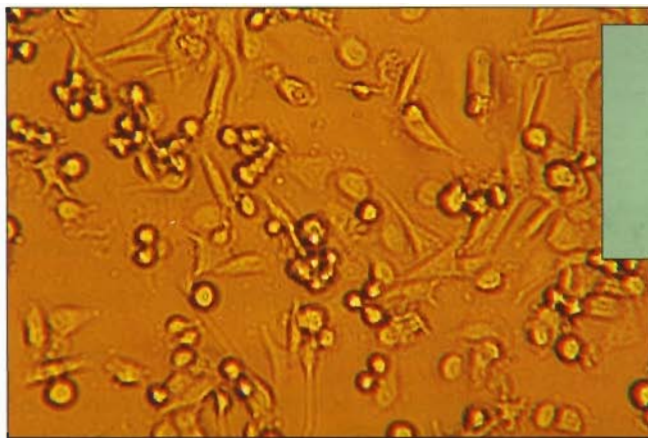
conducted on several types of human cells: *i*) mesenchymal stem cells (MSCs) at different passages obtained from the bone marrow of patients (from non-BEN areas) with hematologic disorders, able to proliferate spontaneously for several months without immortalization, and sensitive to radiation and xenobiotic agents; *ii*) an erythroleukemia cell line (K562), with greater resistance to xenobiotic agents compared with MSCs; and *iii*) a commercial human kidney cell line (HK-2). Cells were exposed to two types of organic compounds: *i*) water extracts of Pliocene lignite from BEN areas and low rank coal from hypothesized PEN areas in the United States (WY and LA) and *ii*) TFU organic concentrates from water in wells and springs from BEN areas and control sites in the Balkans, and from water collected from wells penetrating the coal in WY and LA. Toxicity testing was conducted in standard well plates for periods of 24 to 120 h (26, 27). Exposure levels to organic toxins were controlled by the amount of material added to each well plate and by the duration of the test. Both positive (cells with no addition) and negative (cells with triton-X or dexamethasone solution added) controls were used. Cell viability and proliferation was assessed using a standard MTT assay (28, 29), and visual changes in cell morphology were noted.

Results from these preliminary experiments showed two principal effects. For the HK-2 and K562 cell experiments, lower levels of exposure to organic compounds from coal extracts and TFU concentrates resulted in increased proliferation of the cells relative to controls, while higher levels of exposure resulted in higher rates of cell necrosis relative to controls. Exposure effects (cell proliferation at low exposure and cell necrosis at higher exposure) were most pronounced for the Pliocene lignite extracts and for TFU concentrates from BEN villages in Romania and Serbia. A somewhat lower degree of cell proliferation and necrosis was observed for water samples from coal deposits in the PRB and northwestern LA. The more sensitive MSCs had higher rates of cell necrosis at all levels of exposure to the organic compounds, relative to controls. Cells exposed to the organic compounds also showed morphological changes relative to controls (Fig. 2), including the presence of large vacuoles in the cells.

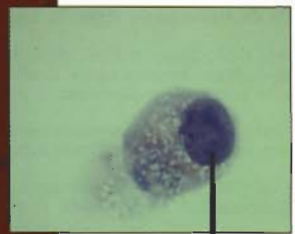
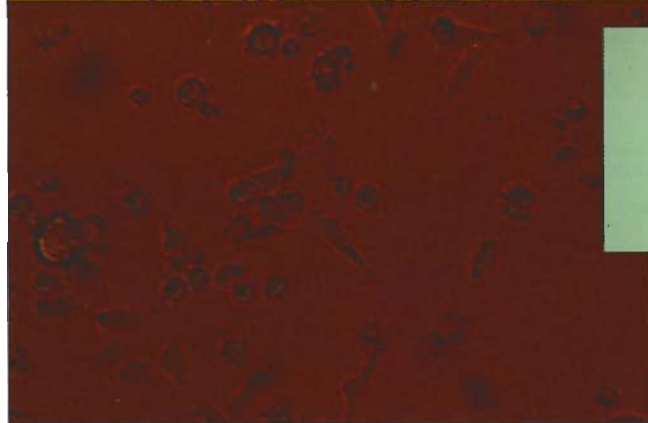
## CONCLUSIONS

The hypothesis implicating coal-derived toxic organic compounds in the etiology of BEN has been tested, and results support the hypothesis. This hypothesis accounts for both the

Normal  
Kidney  
Cells  
HK-2  
Cell Line  
(Control)



Kidney  
Cells  
Treated  
With  
TFU  
Organic  
Concentrate  
From a  
BEN  
Village  
(Treatment)



Note Enlarged  
Vacuole

Figure 2. Morphological effects of exposure of human kidney cell line (HK-2) to organic matter from tangential flow ultrafiltration (TFU) concentrate isolated from a water supply well in a BEN village in Serbia. Note morphological difference between the control (top) and the TFU treated cells. Tangential flow ultrafiltration treatment also produced excessive cell proliferation at low dosage, and cell necrosis at high dose.

geographic restriction of BEN, and many of its medical features. Well water from BEN villages contain higher numbers and concentrations of potentially toxic extractable and HMW organic compounds compared with controls. Study results do not support involvement of inorganic substances (except for the possible involvement of nitrate as a cofactor) in water supplies in BEN etiology.

The concept of PEN or BEN-like diseases (especially RPC) that occur outside of the Balkans is supported by preliminary geochemical results from the United States in states with high rates of RPC and low rank coal deposits (LA and WY). Renal disease may also be linked to lignite-containing areas in northern Portugal (Deolinda Flores, Universidade do Porto, Portugal, personal communication).

Preliminary toxicology studies exposing different types of human cell cultures (including kidney cells) to TFU concentrates from BEN wells/springs, and from areas of high RPC in the United States (LA and WY), showed a range of effects, including excessive cell proliferation at lower doses, and cell necrosis at higher doses, relative to controls. These results are consistent with both the cell necrosis associated with BEN, and the occurrence of RPC in BEN and PEN. Tangential flow ultrafiltration concentrates also induced changes in cell morphology, especially the development of large vacuoles within the cells. Additional cell line toxicology studies and animal experiments (rats) with TFU concentrates, and studies of the effects of organic compounds in TFU concentrates on lecithin : cholesterol acyltransferase activity, which is low in BEN patients (29) are currently under way.

Diseases that are like BEN (kidney nephropathy and RPC) linked to toxic organic compounds derived from coal in drinking water supplies may be widespread. This may also include toxic organic compounds in peat water used as water supplies. Ongoing work is exploring the occurrence and etiology of PEN as a global issue in medical geology, focusing on areas

where low rank coals and populations using untreated well water occur (e.g. India, Turkey, China, Portugal).

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# Health Impacts of Coal: Facts and Fallacies

## INTRODUCTION

Coal has contributed enormously to the advance of civilization by providing an abundant, inexpensive, and convenient source of energy. Concurrent with its contributions, coal has extracted a high cost in terms of environmental damage and human health impacts. Coal will remain a key component of the global energy mix for decades to come as well as a major source of global pollutants. Despite its high media profile, misconceptions about coal abound, especially with regard to its human health impacts. Coal also provides several excellent examples of how a geologic material and human health intersect in a variety of surprising ways. Unfortunately, the links between coal use and human health are distorted by a great deal of ignorance and misinformation. This paper discusses the facts and fallacies of the direct health impacts caused by coal (1, 2). There are a number of important health issues caused by coal that fall outside the scope of this review. The health impacts of particulates emitted from coal combustion have received substantial attention since the groundbreaking work of Wilson et al. (3), and through the recent discussions by Davis (4) and Freese (5). The indirect health impacts of coals through their contributions to global climate change, respirable particulates, acid rain, and acid mine drainage are also beyond the scope of this review. Greb et al. provide an excellent general overview of the environmental impacts of coal (6).

The potential for health impacts caused by exposure to trace elements has received considerable attention for the past quarter of a century. The US Environmental Protection Agency conducted an extensive study of this issue and concluded (7) that, with the possible exception of mercury, there was no compelling evidence of health impacts caused by the emission of trace elements from coal-burning electric generating utilities. Nevertheless, documented examples do exist of health impacts caused by trace elements emitted by coal combustion. Bencko and Symon (8) described hearing problems in children living near a power plant burning high arsenic coal in the former Czechoslovakia. But, perhaps the most significant example of health impacts caused by trace element release from coal use occurs in Guizhou Province, southwest China, where millions of people suffer from dental and skeletal fluorosis and thousands suffer from arsenic poisoning due to mobilization of these elements by burning mineralized coals in unvented or poorly vented stoves (Figs. 1a and b).

## Health Impacts of Residential Coal Use

Zheng et al. (9) describe chronic arsenic poisoning, affecting several thousand people in Guizhou Province, PRC. Those affected exhibit typical symptoms of arsenic poisoning including hyperpigmentation (flushed appearance, freckles), hyperkeratosis (scaly lesions on the skin, generally concentrated on the hands and feet; Fig. 1a), Bowen's disease (dark, horny, precancerous lesions of the skin), and squamous cell carcinoma.

Belkin and coworkers (10, 11) conducted detailed chemical and mineralogical characterization of coal samples from this region and found several samples with >30 000 ppm arsenic. This is more than 1000 times the average and 15 times the maximum concentration of arsenic in nearly 10 000 coal samples from throughout the United States (12). The effects of burning these mineralized coals in a residential environment

are further exacerbated by the practice of drying crops directly over the coal fires.

Zheng et al. have shown that chili peppers dried over open coal-burning stoves may be a principal vehicle for the arsenic poisoning (9). In the autumn it is commonly cool and damp in the higher elevations of Guizhou Province. It is common practice for the residents of this region to dry their corn and chili peppers directly over these coal fires.

Fresh chili peppers have less than 1 part per million (ppm) arsenic. In contrast, chili peppers dried over high-arsenic coal fires can have as much as 500 ppm arsenic. Significant amounts of arsenic may also come from other tainted foods, ingestion of dust (samples of kitchen dust contained as much as 3000 ppm arsenic), and from inhalation of indoor air polluted by arsenic derived from coal combustion. The arsenic content of drinking water samples was not considered to be a significant contributing factor.

The health problems caused by fluorine volatilized during domestic coal use are far more extensive than those caused by arsenic. More than 10 million people in Guizhou Province and surrounding areas suffer from various forms of fluorosis (13), and coal combustion induced fluorosis has also been reported from 13 other provinces, autonomous regions, and municipalities in China (14). Typical signs of fluorosis include mottling of tooth enamel (dental fluorosis; Fig. 1b) and various forms of skeletal fluorosis including osteosclerosis, limited movement of the joints, and outward manifestations such as knock-knees, bowlegs, and spinal curvature.

The cause of this type of fluorosis is similar to that of arsenic poisoning in that the disease is derived from foods dried over coal-burning stoves. Zheng and Huang have demonstrated that adsorption of fluorine by corn dried over unvented ovens burning high-fluorine (>200 ppm) coal is the probable cause of the extensive dental and skeletal fluorosis in southwest China (13). The problem is compounded by the use of clay as a binder for making briquettes. The clay commonly used is a high-fluorine (several hundred parts per million) residue formed by intense leaching of the limestone substrate. Ando et al. estimated that 97% of the fluoride exposure came from food consumption and 2% from direct inhalation (14).

Although there is considerable concern about the health effects of mercury and the proportion of anthropogenic mercury in the environment (15), to date there has been no direct evidence of health problems caused by mercury released from coal, but there are circumstances where poisoning from mercury released from coal combustion may be occurring. In a Guizhou Province village, many elderly villagers exhibit loss of vision. Mineralogical analysis of the coal being used in the homes of people having visual impairment revealed abundant mercury minerals. Chemical analysis of a coal sample being used in this village indicates a mercury concentration of 55 ppb, about 200 times the average mercury concentration in US coals (12). Because mercury acts as a neurotoxin, the loss of vision may be related to the high levels of mercury released from the coal used in this village.

Zheng et al. report nearly 500 cases of human selenosis in southwest China that are attributed to the use of selenium-rich carbonaceous shales known locally as "stone coal" (16). The stone coals may contain as much as several thousand parts per million of selenium. This selenosis is attributed to emission of



**Figure 1. (a) Hyperkeratosis caused by exposure to arsenic mobilized by burning mineralized coals in a residential environment. (b) Dental fluorosis caused by exposure to arsenic mobilized by burning mineralized coals in a residential environment.**

selenium from the combustion of the stone coal and the practice of using combustion ash as a soil amendment. This process introduced large amounts of selenium into the soil and resulted in selenium uptake by crops. Symptoms of selenium poisoning include hair and nail loss.

The health problems caused by trace element release by coal combustion can be minimized or eliminated in several ways. Coal quality databases and maps illustrating the coal quality variations can help to identify coal deposits with high trace element contents. Belkin et al. describe a simple test kit than can be used at the mine to test the coal for its arsenic content (17). Improved economic conditions could help to alleviate these problems by allowing villagers to purchase commercial coal, briquettes, and modern stoves.

### A HEALTH BENEFIT OF COAL COMBUSTION

Coal combustion is a dirty process. In addition to emitting potentially harmful elements such as arsenic, fluorine, selenium, mercury, and lead, the combustion process also releases particulates, acid gases, and organic compounds, all potentially harmful to human health. It is therefore highly surprising to find a beneficial health impact of coal combustion.

Wang and others report on the occurrence of iodine deficiency disorders (IDD) in Guizhou Province, PRC (18). Communities in the province in which coal is the principal source of residential fuel have a low incidence of IDD whereas communities that primarily rely on wood have a far greater incidence of IDD. Chemical analyses of the fuels indicate that the coal is markedly enriched in iodine. Burning the coal in the home to dry crops mobilizes the iodine and may provide a significant health benefit in preventing IDD. We use this example not to advocate the use of coal to prevent IDD but to illustrate that there is still much to learn about the impact of coal use on human health.

### HEALTH IMPACTS OF IN-GROUND COAL

An unusual situation exists in the Balkans where there may be health problems caused by coal in the ground. Lignite has been cited as a contributory factor in a severe, debilitating kidney disease with associated urinary tract cancers (18, 19, 20). The disease, known as Balkan endemic nephropathy (BEN), occurs in clusters of villages in the former Yugoslavia and Romania. Since records were kept in the 1950s, as many as 100 000 people in the endemic villages are believed to have died from kidney failure and related health problems. In all of the endemic villages a common factor is that the primary source of drinking water is wells

completed in lignite aquifers. Analysis of the well waters has revealed that wells in BEN villages have greater concentrations and numbers of organic compounds compared to control sites. Many compounds observed in the well water from BEN villages are potentially toxic (e.g., heterocyclic compounds and aromatic amines, and similar compounds have been water-leached from these lignites in the laboratory. It has been postulated that these organic compounds, leached from the lignites, are significant contributory factors in causing BEN (21). Recent studies have demonstrated a similar suite of organic compounds in water from wells underlain by lignites in Louisiana in the United States. This area is known to have one of the highest incidents of renal and pelvic cancers in the United States. In Portugal, the region where lignites were formerly mined coincides with the highest incidence of kidney disease in the country.

### HEALTH IMPACTS OF UNCONTROLLED FIRES

There are tens of thousands of uncontrolled burning coal seams and coal waste piles around the world (22). They are especially prevalent in China, India, and South Africa (Figs. 2a and 2b). These fires, which are started intentionally or by spontaneous combustion, mine fires, and lightning strikes, release enormous amounts of pollutants that are a potential environmental and human health hazard. On a global scale, the emissions of large volumes of greenhouse gases from burning coal beds may contribute to climate change that alters ecosystems and patterns of disease occurrence. On regional and local scales, the emissions from burning coal beds and waste banks of acidic gases, particulates, organic compounds, and trace elements can contribute to a range of respiratory and other human health problems. The health impacts of uncontrolled coal fires are poorly understood. Although there are few published reports of health problems caused by these emissions, the potential for problems can be significant (23). In India, large numbers of people have been displaced from their homes because of health problems caused by emissions from burning coal beds. Potentially toxic elements such as arsenic, fluorine, mercury, and selenium are commonly enriched in coal deposits. As described previously, volatilization of these elements from coal has caused severe health problems in China. Burning coal beds also can volatilize these elements, which then can be inhaled, or adsorbed on crops and foods, taken up by livestock or bioaccumulated in birds and fish. Emissions from these fires also include high concentrations of benzene, toluene, xylene, and ethylbenzene (24). This is a potentially significant coal-related health problem that needs further study.



## Black Lung Disease

Although the incidence of coal worker's pneumoconiosis (CWP: black lung disease), a progressive, debilitating respiratory problem caused by inhalation of coal dust, has decreased dramatically in the United States, it still takes a heavy toll on coal miners in developing countries. For example, an estimated 600 000 Chinese coal miners are suffering from CWP. The number of Chinese coal miners suffering from CWP is estimated to increase by about 70 000 each year. For more than 100 years it has been assumed that black lung disease was caused by the inhalation of the black pulverized particles of coal. Recent research, however, has shown that CWP may be initiated not by the coal particles but by inhalation of pulverized pyrite, a common coal mineral (25). The pyrite dissolves in the lung fluids, releasing iron sulfate and strong acids that irritate the lung tissues. Particles (coal dust, quartz, clay, pyrite, etc.) that then contact the irritated tissues may then cause the fibrosis leading to decreased oxygen exchange capacity. Thus, knowledge of the mineral composition of the coal may be a key parameter in anticipating the incidence of CWP. Information on the mineralogy of the coal being mined may provide essential data needed to protect the health of the miners in cost-effective ways, thus reducing the enormous financial burden of health care and lost productivity.

## IS FLY ASH A HEALTH THREAT?

Combustion of coal produces enormous amounts of fine-grained respirable particles called fly ash. Worldwide several hundred million tons of fly ash is generated annually.

The trace element concentration of the fly ash is commonly enriched by about a factor of 10 compared with coal—mercury, selenium, and fluorine are exceptions because of their volatility. Moreover, the finer particle sizes (those more readily inhaled and retained in the lung) have the highest concentrations of most trace elements. Thus, exposure to coal fly ash on a regular basis could present a significant health threat. Fortunately, most modern coal burning power plants have sophisticated pollution control equipment that captures up to 99.5% of the fly ash produced during combustion. Environmental and health problems can be minimized by proper use or disposal of these coal combustion by-products. As mentioned previously, following extensive studies, the US Environmental Protection Agency concluded that, with the possible exception of mercury, there was no compelling evidence of health impacts caused by the emission of trace elements from coal-burning electric generating utilities (27).

There is one aspect of fly ash chemistry that deserves further attention. Recent studies have shown that some fly ash samples contain a very high proportion (as much as 50%) of hexavalent chromium, a very potent carcinogen (26). Moreover, all of this hexavalent chromium is water soluble and would readily be liberated in lung and stomach fluids.

## RADIOACTIVITY FROM COAL: AN UNLIKELY PROBLEM

Finally, not all of the health concerns attributed to coal are valid. Periodically, there have been reports in the scientific and public literature about the threat of radioactivity from coal and coal combustion products. One of the more serious accusations is that young boys playing near disposal sites of coal combustion by-products will be made sterile by the radiation. This is pure fabrication. Although there are coals with relatively high concentrations of uranium, these are rare and none are currently being mined in the United States. The levels of radionuclides in coal and coal combustion by-products are generally low to modest, commonly in the same range as many surficial rocks and soils (27). Radon, a daughter product of uranium decay, however, may present a legitimate health concern to coal miners working in poorly ventilated mines.

## CONCLUSIONS

The direct health problems caused by coal and coal use are generally local and potentially severe. Nevertheless, once identified, practical solutions are available. For people living in areas where high quality coal is burned in modern boilers using the best available pollution control technology and sensible coal combustion by-product disposal practices, the health threat is probably minimal. More research is necessary to assess the effects of long-term, low level exposure to effluents from coal-burning power plants.

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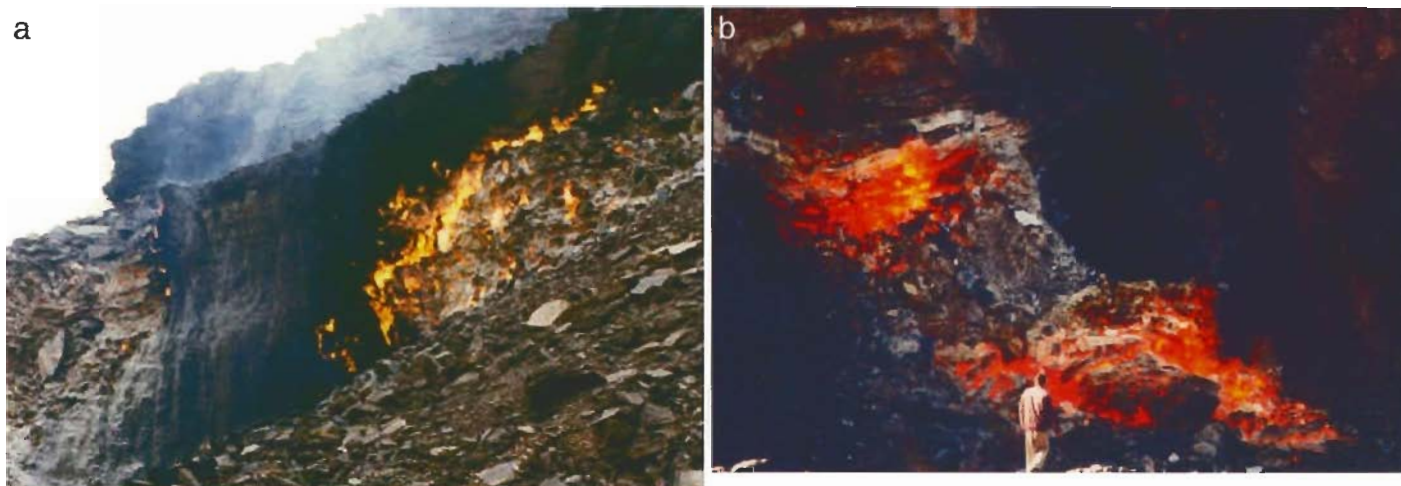


Figure 2. (a) Jharia coalfield, India. (b) Surface mine fire, northern China

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# Metal Biology: Aspects of Beneficial Effects

## METAL BIOLOGY

The biology of metals is not a new concept. It may be expressed as trace element biology, which in a sense is a broader concept. Nevertheless, in this presentation we also include nonmetals in metal biology. Trace elements are often described as minerals—from a fundamental point a misconception. Depending on the platform from which trace elements are defined we find different approaches. An analytical chemist would probably define them as elements appearing in concentrations below 100 mg kg<sup>-1</sup>. If a biologist is asked, you would most certainly be presented with an exclusion definition.

We start with excluding the major elements of life: hydrogen, carbon, nitrogen, and oxygen. In the next phase the minor elements sodium, magnesium, potassium, and calcium as well as phosphorus, sulfur, and chlorine are excluded. In addition, the noble gases helium, neon, argon, krypton, xenon, and radon are excluded for obvious reasons. At the end of this process, we have excluded 17 of the elements. The number of naturally occurring elements is disputed but here we will assume that they are 90. Seventy-three of these elements are defined as trace elements.

The fascinating aspect of these two different approaches in defining trace element is that both sides arrive at about the same elements, at least with occurrence in living systems as a basis. There are further distinctions among trace elements that have to be accounted for. Not all 73 elements are essential for life. Significant unanimity is reached for 14 or 15 elements.

## ESSENTIALITY AND DOSE RESPONSE

What is essential for life is not easy to express. During the last decades various definitions have emerged, some very strict and others primarily pragmatic. The current definition of essentiality is that an element is considered essential to an organism when reduction of its exposure below certain limit results consistently in a reduction in a physiologically important function, or when an element is an integral part of an organic structure performing a vital function in the organism.

What is said above has the implication that the dose response of nonessential elements goes from normal function to malfunction and eventually to death. For essential elements the dose response shows a different behavior. At low doses, deficiency occurs and with increasing doses we approach an interval of safe and adequate intake (dose). With even higher doses, toxicity appears, and death may result. As Paracelsus claimed, toxicity is only a matter of dose. Even essential trace elements in excessive amounts can cause toxicity (Fig. 1).

## IRON: SAVIOR AND THREAT

If it is meaningful to classify essential trace elements, we would probably put iron among the most important ones. Most people know that iron is necessary for the transport of oxygen by hemoglobin in the red cells. However, this is only one of the important tasks performed by iron in interaction with certain biomolecules. Iron functions are of two major classes. Either it performs the function as an ion, most often in conjunction with sulfur in iron-sulfur proteins as well as in some iron proteins using simple N/O coordinating ligand, or as an integral part of the heme group. The biosynthesis of heme takes place in mitochondria (Box 1). It is synthesized through insertion of iron into protoporphyrin by ferrochelatase.

The start of the synthesis is different in eukaryotes and prokaryotes (Box 1) as compared with plants. Glycine and succinyl-CoA is combined with  $\delta$ -aminolevulinic acid in eukaryotes and prokaryotes by the enzyme  $\delta$ -aminolevulinic synthetase. In plants glutamate is linked to a specific tRNA and successively acted upon by ligase producing glutamyl-tRNA. This compound is transferred to glutamate  $\delta$ -semialdehyde by a reductase (1). Then an amino transferase catalyzes the formation of  $\delta$ -aminolevulinic acid. The enzymatically driven sequence is thereafter identical for plants and animals until the production of protoporphyrin IX. In prokaryotes and eukaryotes, as well as in plants, iron is incorporated through the catalysis by ferrochelatase to form heme. Plants possess the alternative pathway of incorporating magnesium catalyzed by magnesium chelatase and the end product is chlorophyll (2).

Heme proteins are very important in biology. It is definitely not only hemoglobin and myoglobin, the two oxygen-transporting proteins in animals, that are of vital interest. Myoglobin is a smaller molecule relative to hemoglobin and is the principal oxygen storage protein. An interesting property of hemoglobin, in addition to its oxygen-binding ability, is its enzymatic activity. It has been thought that the oxygen carrier function was so specialized that globins were not recruited to new tasks; however, it has recently been found that the globin of some marine worms (*Amphitrite ornata*) has evolved into a powerful peroxidase, more precisely dehaloperoxidase. This enzyme catalyzes the oxidative dehalogenation of polyhalogenated phenols in the presence of hydrogen peroxide at a rate at least ten times faster than all known halohydroxylases of bacterial origin (3). Catalase is an enzyme that can transfer hydrogen peroxide into water, a process of utmost importance in the metabolism of molecular oxygen to water in the mitochondria.

Cytochromes constitute a group of heme proteins with distinctive visible-light spectra that function as electron carriers from biological fuels to oxygen. Thus they are vital members of the mitochondrial electron-transfer chain. In addition, the cytochromes are also essential components in plant chloroplast for photosynthesis. It is the ability of the iron center to undergo reversible Fe(III)  $\leftrightarrow$  Fe(II) changes to allow them to act as electron-transfer centers.

Cytochrome P-450 enzymes are heme proteins that function as monooxygenases to catalyze the insertion of oxygen into a C-H bond of an aromatic or aliphatic hydrocarbon (Box 1). Examples of the biological functions of cytochrome P-450 are drug metabolism and steroid synthesis (Box 1). One of the many interesting aspects of cytochrome P-450 is that some are inducible, which means that following exposure of the cell to an inducing chemical enzyme activity increases, in some cases several orders of magnitude (4).

There are also iron-activated enzymes. The most prominent example of this class of enzymes is heme oxygenase, which has evolved to carry out oxidative cleavage of heme, a reaction essential in several physiological processes as diverse as iron reuse and cellular signaling in mammals and synthesis of essential light-harvesting pigments in cyanobacteria (Box 1) and higher plants, as well as the acquisition of iron by bacterial pathogens (5).

The porphyrin ligand environment of iron that occurs in hemoglobin and myoglobin is also important in redox enzymes (Box 1). Iron-sulfur clusters were not familiar to inorganic

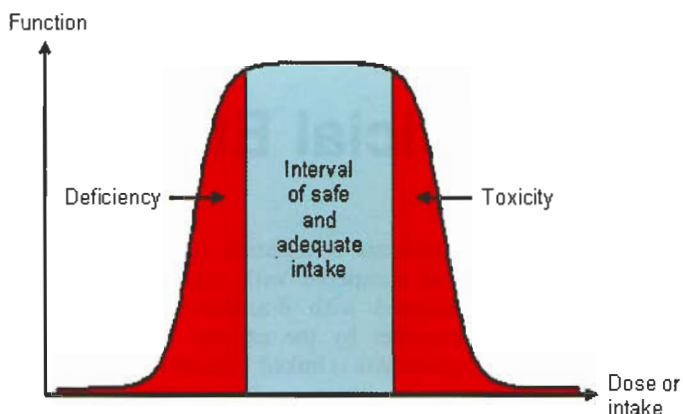


Figure 1. Dose-response relationship of essential trace elements.

chemists prior to recognition of their biochemical importance. Iron-sulfur clusters are simple inorganic groups that are contained in a variety of proteins having functions related to electron transfer, gene regulation, and environmental and substrate activation. Biological Fe-S clusters, however, are not formed spontaneously, but a consortium of highly conserved proteins is required for both the formation of Fe-S clusters and their insertion into various protein partners. Examples of proteins with Fe-S clusters in the electron transfer are ferredoxin and Rieske ferredoxin. Involved in gene regulation are, e.g., iron regulatory protein-I and superoxide regulatory system (6).

Transferrin originally was the name of the serum protein that binds and transports iron for delivery to cells. Today, it is the name applied to a wider family of homologous (Box 1) proteins that includes serum transferrin, lactoferrin, ovotransferrin, and melanotransferrin (7). Transferrins seem to be involved in the homeostatic control of free iron in all the places where it might be found. The two iron-binding centers of serum transferrin are very specific for iron(III) and have a binding constant of about  $10^{20}$ . Lactoferrin is an iron-binding protein that binds iron even more tightly than transferrin. It is present in milk, many other exocrine secretions, and white blood cells. One of the first functions attributed to lactoferrin was the ability to inhibit bacterial growth and viral infection. It is thought that lactoferrin is able to sequester iron from certain pathogens, which inhibits their growth. Another important function is its ability to stimulate the release of the neutrophil-activating polypeptide interleukin-8. This suggests that lactoferrin might function as an immunomodulator for activating the host defense system (8).

Hemopexin is a recycler and transporter of heme. Turnover of heme proteins, notably hemoglobin, leads to the release of heme into extracellular fluids with potentially severe consequences. Like free iron, heme is a source of essential iron for invading bacterial pathogens and is highly toxic because of its ability to catalyze free-radical formation (Box 1). Protection is given by hemopexin, a 60-kDa serum glycoprotein that sequesters heme with very high affinity from the bloodstream; transports it to specific receptors on liver cells, where it undergoes receptor-mediated endocytosis; and releases the bound heme into cells. It thus serves both to protect against heme toxicity and to conserve and recycle iron (7).

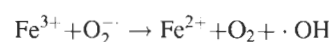
Ferritin and hemosiderin are the most efficient classes of proteins with a high capacity to store iron. Ferritins are found in bacterial, plant, and animal cells. They form hollow, spherical particles in which up to 4500 iron atoms can be stored as iron(III). The biosynthesis of ferritin is controlled by the level of iron in the cell via the iron regulatory protein (9). Hemosiderin is another iron-storage complex; however, knowledge of its structure is minimal. It is found solely in cells, in contrast to ferritin, which can also be found in the circulation. Iron present in hemosiderin deposits is poorly available to

provide iron on demand. The storage complex is found in macrophages and appears to be especially abundant following hemorrhage; thus, its formation might be related to phagocytosis of red blood cells and hemoglobin (10).

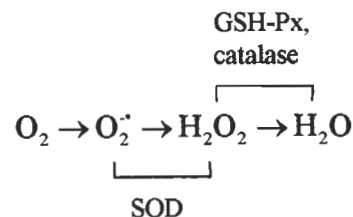
Two famous, or rather notorious, chemical reactions, in which radicals are produced, are Fenton and Haber-Weiss. These reactions can explain why certain metals in free form are especially malignant. The Fenton reaction is driven in the absence of chelators by Cu(I), Fe(II), Co(II), Ti(III), and Cr(V) ions. For iron the reaction is



Although most metals have a rich redox chemistry not all are able to react with certain oxygen or other substrates and activate them to strongly oxidizing species like the hydroxyl radical ( $\cdot\text{OH}$ ) under physiological conditions. The substrates of Fenton and Haber-Weiss reactions is dioxygen and two of its metabolites, hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) and the superoxide anion ( $\text{O}_2^-$ ). After a Fenton reaction, the newly oxidized metal ion can retain its original oxidation state by reduction in a Haber-Weiss reaction.



There is always a source of substrates due to the metabolism of dioxygen in the mitochondria. This process is potentially very dangerous and is therefore put under strict control. The end product of the reduction is water and the reaction is catalyzed by cytochrome oxidase, which is a heme-dependent enzyme. Unfortunately, the reaction cannot go directly to water because this would demand that four electrons be put on dioxygen at the same time and this is chemically impossible. Instead, there is a sequence of one-electron transfers that produces reactive oxygen species. Evolution has provided means to take care of these reactive products by a series of enzymes. The overall reaction, without all details, including these defense systems, is



where GSH-Px is glutathione peroxidase and SOD is superoxide dismutase. The latter enzyme catalyzes a dismutation reaction (Box 1), in which one superoxide anion is oxidized and another superoxide anion is reduced and the product is hydrogen peroxide and dioxygen ( $\text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$ ). The hydrogen peroxide is then decomposed to water and dioxygen ( $2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$ ), and this reaction is catalyzed either by catalase or glutathione peroxidase.

Radical reactions induced by the presence of free iron ( $\text{Fe}^{2+}$ ) have been suggested to be causing cellular damage could be involved in various diseases such as Parkinson's disease (11, 12), multiple sclerosis (13) and atherosclerosis (14, 15). Even the *Chlamydia pneumoniae* infection is thought to be partly driven by iron (16, 17). Homeostatic mechanisms that control the level of free iron circulating have therefore evolved, and normally the ratio of free to bound iron is maintained at about  $10^{-17}$ .

## ZINC: THE MASTER OF ENZYMES

Zinc has been known to be essential to life since 1869, when it was discovered that it was required by *Aspergillus niger*. In contrast to the metals in the transition area of the periodic table, zinc does not take part in redox reactions. However, it is a very good Lewis acid, and it has a hard metal center and is ideally

## Box 1 Glossary

Acute-phase proteins	Any protein whose plasma concentration increases or decreases by 25% or more during certain inflammatory disorders.
Aliphatic	Organic compounds in which carbon atoms are joined together in straight or branched chains as opposed to aromatic compounds, which include ring structures.
Apoptosis	Programmed cell death.
Aromatic	A compound of hydrogen and carbon with one or more carbon rings.
Chromatin	The complex of DNA and proteins that makes up a eukaryotic chromosome.
Cyanobacteria	Bacteria that obtain their energy by photosynthesis.
Dismutation	Also called disproportionation reaction. A reaction in which a given substance is both oxidized and reduced.
Eukaryotic cell	A type of cell with a membrane-enclosed nucleus and membrane-enclosed organelles; also called eukaryote.
Hemorrhage	Bleeding (severe).
Homology	Similarities in characteristics resulting from a shared ancestry.
Mitochondrion	An organelle in eukaryotic cells that serves as the site of cellular respiration.
Prokaryotic cell	A type of cell lacking membrane-enclosed nucleus and membrane-enclosed organelles.
Radical	An atom or a molecule with one or more unpaired electrons.
Redox	A process in which there is a net movement of electrons from one reactant (reducing agent) to another (oxidizing agent).
Ribosome	A cell organelle constructed in the nucleolus and functioning as the site of protein synthesis in the cytoplasm; consists of ribosomal RNA and protein molecules that make up two subunits.
Steroid	A type of lipid characterized by a carbon skeleton consisting of four rings with various functional groups attached.

suited for coordination of N- and O-donors. The first enzyme to be recognized as a zinc metalloenzyme was carbonic anhydrase, an enzyme essential for respiration in mammals. At present, zinc metalloenzymes have been recognized in all classes of enzymes. Today, more than 300 enzymes are known to be dependent on zinc. Zinc has three types of roles with regard to enzymes: catalytic, cocatalytic, and structural. Carbonic anhydrases are a widely expressed family of enzymes that catalyze the reversible reaction  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{HCO}_3^- + \text{H}^+$ . These enzymes therefore both produce  $\text{HCO}_3^-$  for transport across membranes and consume  $\text{HCO}_3^-$ , which has been transported across membranes (18). In carbonic anhydrase, zinc is catalytic. An example of the structural role of zinc in enzymes is aspartate transcarbamylase. This enzyme catalyzes the first step in pyrimidine biosynthesis, condensation of aspartate and carbamyl phosphate.

Leucine aminopeptidase is a prototypic dizinc peptidase that has been studied intensely. The enzyme is present in animals, plants, and bacteria and has various tissue-specific physiological roles in the processing or degradation of peptides. Human leucine aminopeptidase has been shown to catalyze postproteosomal trimming of the N terminus of antigenic peptides for presentation on major histocompatibility complex class I molecules (19).

Alcohol dehydrogenase is yet another zinc-dependent enzyme, which is our primary defense against alcohol intoxication. There are at least nine different forms of the enzyme in humans, and they are mostly found in the liver. The enzyme catalyzes the transformation of ethanol to acetaldehyde. This product is even more toxic than ethanol. So, this toxic molecule is transformed in the next step by aldehyde dehydrogenase to acetic acid and other molecules that can be used by the cells. Alcohol dehydrogenase also catalyzes the transformation of retinol in the eye to retinaldehyde and by aldehyde dehydro-

genase to retinoic acid (20). There is an additional problem with alcohol dehydrogenase in that it modifies other alcohols, often producing dangerous products. For instance, methanol is converted into formaldehyde, which causes damage to proteins and possibly cancer. Small amounts of methanol cause blindness when the sensitive proteins in the retina are attacked, and larger amounts lead to widespread damage and death (21).

It is by now well established that zinc plays a very important role in gene expression. The importance can be appreciated from the fact that about 25% of the zinc content of rat liver is found in the nucleus, and a significant amount of zinc is incorporated into nuclei *in vitro* (22). Zinc is involved in the process of genetic stability and gene expression in various ways, including the structure of chromatin (Box 1), replication of DNA, and transcription of RNA through the activity of transcription factors and RNA and DNA polymerases, as well as playing a role in DNA repair and programmed cell death (23).

One very important aspect of zinc is the so-called zinc fingers, which were first discovered as the transcription factor IIIA (TFIIIA). TFIIIA is a site-specific DNA-binding protein that plays a central role in controlling the transcription of 5S ribosomal (Box 1) RNA genes in the African toad *Xenopus laevis*. This protein is slightly unusual because not only does it recognize the internal control region of about 45 base pairs in the center of the 5S RNA gene, but also TFIIIA itself is bound to the product. The name zinc fingers was introduced because of the specific interaction between the amino acids cysteine, histidine, and a zinc ion responsible for the formation of the characteristic loop structure. Zinc fingers are generic protein motifs that can mediate DNA-binding and are both widespread and multifunctional. Since first being discovered in the early 1980s, several more zinc-finger proteins have been identified. More than 50 zinc-finger proteins are known today. Additionally, it has been suggested that zinc fingers play a protective role through their prevention of chemical attack by, for example, radicals or reactive oxygen species (24).

Zinc also takes part in the defense against excessive amounts and following damage of certain metals, and it does so through the interaction with metallothionein. These proteins are ubiquitous and constitute a superfamily. It is challenging that very few suggestions as to the biological functions of metallothionein have emerged, although the protein has been extensively studied for decades. The main consensus seems to be that it has a role in the detoxification of metals. Recent studies have produced strong evidence to support the idea that metallothionein functions as a metal chaperone for the regulation of gene expression and for the synthesis and functional activity of metalloproteins and metal-dependent transcription factors (25). It has been suggested that a biological function of metallothioneins is to provide redox functions to the cells. Although zinc, copper, cadmium, mercury, gold, and bismuth are all metals that induce metallothionein, zinc is the primary physiological inducer. Zinc and copper are essential trace elements and the other metals are environmental toxicants; however, copper in nontoxic concentrations does not induce metallothionein (26).

There is no single factor regulating metallothionein synthesis in inflammation; instead, a complex interrelationship exists between factors that, in combination and in different tissues, act synergistically on metallothionein gene transcription. Nucleotide sequences other than metal-responsive elements respond to glucocorticoids, interleukin-6, phorbol esters, and hydrogen peroxide. Many of the acute-phase proteins (Box 1) appear to be regulated by combinations of the same factors that include catecholamines and glucocorticoids, as well as the cytokines interleukin-6, interleukin-1, tumor necrosis factor  $\alpha$ , and  $\gamma$ -

interferon. Unlike other acute-phase proteins, metallothionein induction by inflammatory mediators has been found to be conditional upon the presence of zinc. Reactive oxygen species generated during the inflammatory response may induce metallothionein through multiple pathways, including direct stimulating an antioxidant response element and specific metal-responsive elements in the promoter region as well as by events associated with various second-messenger protein kinase pathways.

Several forms of disordered glucose metabolism are collectively referred to as diabetes. In insulin-dependent diabetes mellitus (IDDM), there is a destruction of the beta cells of the islets of Langerhans in the pancreas, most often on an autoimmune basis, which results in no insulin being produced. Without insulin, muscle, fat, and liver cells cannot transport glucose from the blood to the intracellular space. Intracellular starvation ensues, with fats becoming the primary intracellular energy source. This form of energy generation results in the production of ketone bodies and organic acids, primarily acetoacetic and beta hydroxybutyric acids, resulting in the development of severe metabolic acidosis (27). There is an intriguing relation between zinc and insulin regarding the storage of insulin in granulae of the pancreatic islets. Although insulin circulates in the blood and binds to the receptor as a monomer, it forms dimers at micromolar concentrations, and in the presence of zinc ions it further assembles to hexamers. The zinc-metallothionein complex in the islet cells may provide protection against free radicals produced in the cells from any cause and certainly the immune-mediated, cytokine-provoked oxidative stress would be a significant stress. The more depleted the intracellular zinc stores, the less able the cell is to defend itself against this oxidative load.

Nutritional factors, including zinc, are important for the function of the immune system. Several possible hypotheses can be offered regarding the mode of action of zinc on immune function. Zinc may be necessary for the activity of some immune system mediators such as thymulin, a nonapeptidic hormone secreted by thymic epithelial cells that requires the presence of zinc for its activity. The peptide promotes T-lymphocyte maturation, cytotoxicity, and IL-2 production. Thymulin production in both animals and humans is dependent on plasma zinc concentrations. Zinc could also be critical for the activity of some cytokines; for example, it has been demonstrated that the production or activity of IL-1, IL-3, IL-6, IFN- $\gamma$ , and TNF- $\alpha$  are affected by zinc deficiency. Zinc could contribute to membrane stabilization by acting at the cytoskeletal level. Additionally, zinc is a major intracellular regulator of lymphocyte apoptosis (Box 1) (28).

## SELENIUM AND IODINE: YOUNG AND OLD TRACE ELEMENTS

These trace element are found in the nonmetal area of the periodic table. Although they are neighbors, significant differences exist in their chemical behavior. Selenium is a nonmetal with semiconductor properties and iodine as a halogen. The biological history of iodine can be traced back to the beginning of the nineteenth century when a physician named Jean-Francois Coindet used various iodine solutions to treat goiter (29). Another halogen, although more reactive than iodine, fluorine was also quite early connected to goiter. It was shown that feeding a dog with sodium fluoride caused goiter to appear (30). The human essentiality of iodine was established in 1850.

The scientific community's appreciation of the trace element selenium has more or less undergone a metamorphosis. The toxic effects of selenium were first discovered in the 1930s when livestock ate certain plants with unfortunate results. This problem, mistakenly called "alkali disease," occurred in an acute form following the consumption by range animals of

some wild vetches of the genus *Astragalus*, which accumulated toxic amounts of selenium from the soil (31). A historical aside is that it is thought that General Custer might have survived his trip to the Little Bighorn if reinforcements had not been delayed by pack animals that were apparently suffering from selenium-induced lameness. In 1943, selenium was even considered to be a carcinogenic element (32). It was some years before selenium was recognized as an essential trace element (33). Not very long ago, Clark et al. showed in a large study that selenium supplementation prevented a series of cancer forms (34).

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# Mobilization of Mercury and Methylmercury from Forest Soils after a Severe Storm-Fell Event

## INTRODUCTION

Mercury is an element with a complex biogeochemical cycle in air, soils, water, and biota; mercury originates from both natural and anthropogenic sources. Although mercury is a naturally occurring element, human activities have increased levels in the environment by about a factor of three globally (1). Humans are exposed to mercury through industry, artisanal gold mining, dental amalgam, and fish consumption. The main concern of mercury in the environment is associated with elevated concentrations of methylmercury in fish because methylmercury bio-accumulates in freshwater fish at concentrations that may be harmful to human health. The main health concern refers to neurological damage, and unborn fetuses are especially sensitive to low doses of methylmercury.

In boreal regions, mercury in the environment is to a large extent accumulated in soils and sediments with only small fractions available for uptake in aquatic food chains. A large fraction of this mercury is of natural origin. However, external factors such as forestry operations (2, 3) and storm events can affect the environmental biogeochemistry of mercury and increase the risks of bioaccumulation in aquatic ecosystems. In addition to direct atmospheric deposition, mercury leaching from forest soil is the most important source of mercury in surface waters, and external factors affecting the forestry system may therefore result in a significant increase in the load of mercury on streams and lakes. This study focuses on two examples where an increased mobilization of mercury and methylmercury from forest soils to aquatic ecosystems has been observed: forestry operations and storm-felling.

## Forestry

Studies have shown that leaching of total mercury (THg) and methylmercury (MeHg) from forest soil may increase following the use of heavy machinery in forests (3) and clear-cutting followed by soil scarification (2). Large increases of leaching (a factor of two to four) of methylmercury via runoff water have been observed in affected forested catchments in Sweden and Finland. These studies indicate that logging and soil disturbances can result in protracted (>5 years) and significant increased levels of primarily MeHg in the runoff water from forests. The forest regeneration period following logging is critical because the soil conditions of clear-cut areas are more favorable for mobilization of mercury, particularly MeHg. The soil conditions in clear-cut areas are warmer and moister compared with growing forests because of decreased transpiration and increased sun exposure when the trees have been removed. These conditions result in a higher groundwater level and an increased amount of easily decomposable organic material. These conditions will change the hydrological pathways to enhance leaching of MeHg already present in the soil and may also stimulate methylation of mercury to MeHg. Methylmercury mobilization is most likely caused by the formation of anaerobic zones in the soil where conditions for methylation of mercury by sulfate reducing bacteria are favorable.

## Storm Events

The observations of increased leaching of mercury due to forestry led to concerns of the impacts of the storm Gudrun, which occurred in the winter of 2005, causing extensive damage to the forests in many regions in south Sweden through massive windthrow. Very extensive clearing-up operations were initiated after the storm when large areas of storm-felled forests had to be cleared. Mercury leaching from these storm-felled areas is expected to be of the same magnitude as from clear-cuts and consequently, the drastic increase in deforested areas following the storm is expected to result in increased levels of mercury leaching to surface waters.

## METHOD

A preliminary assessment of the potential for increased MeHg loadings on the surface waters in this region was carried out during the first year after the event. Flux calculations of the leaching of mercury and MeHg were carried out using a geographical information system (GIS)-based model to identify areas at risk of significant increases of mercury leaching due to the storm. Furthermore, a sampling program for mercury in runoff water in storm-felled areas was initiated.

## Flux Calculations

The potential increase in the leaching of total mercury and MeHg from forest soils to surface waters in the south of Sweden following the storm event (Gudrun) was estimated in a GIS-based model (50 × 50 m grid resolution). The GIS-database contained information on catchment areas and configuration, hydrology, and landcover data, together with data on typical mercury levels in runoff waters from clear-cuts and growing forests. Remote sensing data of clear-cut areas before and after the storm event were used to identify new clear cut areas from the storm.

Clear-cut areas in the south of Sweden were estimated to constitute approximately 3.9% of the forest area, based on land cover data derived from satellite images (4). When these data were complemented with data (satellite images) of deforested areas from the storm, clear-cut areas in the study region were estimated to have increased by 64% to 6.3% of the total forest area. This increase was not homogenous across the region because variations in storm damage occurred in the south of Sweden. The increase in clear-cut areas following the storm was predicted to result in an increase in leaching of mercury to surface waters, assuming that the leaching levels of mercury from the storm-felled areas are similar to those of normal clear-cuts.

Leaching coefficients for THg and MeHg were derived from measurements in runoff water from growing forests and conventional clear-cuts (Table 1). Few studies of mercury leaching (THg and MeHg) in runoff water from growing forests in Sweden exist. In the south of Sweden, measurements of THg have only been investigated in a few streams, and studies of MeHg are even rarer. The leaching coefficients of

**Table 1. Leaching coefficients applied in this study for mercury (THg and MeHg) from forest soil (growing forest and clearcut).**

	Growing forest			Clear-cut		
	Median	Min	Max	Median	Min	Max
THg (ng L <sup>-1</sup> )	4.1	0.59	36.3	7.5	2.8	19
MeHg (ng L <sup>-1</sup> )	0.12	0.002	6.15	0.51	0.03	11

THg and MeHg in growing forests applied in this study are based on data from measurements in eight and four streams, respectively, from 1987 onward. Leaching coefficients of THg and MeHg from clear-cuts are based on 14 clear-cut areas and 1 storm-felled area (>50%–75% storm felled) in the south of Sweden. In this study, mercury leaching from storm-felled areas is assumed to be similar to that of normal clear-cuts.

### Measurements

Measurements of mercury are ongoing in surface waters at a selected number of sites in the storm affected area to monitor the effects of the storm on surface waters. Runoff samples for analyses of THg and MeHg were collected manually using 125-mL acid-leached Teflon bottles. Samples were immediately brought to the IVL laboratory and preserved with 0.5 mL 30% HCl (Merck Suprapur). For analysis of THg, the samples were oxidized using BrCl for at least 8 h. Excessive BrCl was removed by addition of 0.5 mL NH<sub>2</sub>OH. A sample aliquot was transferred to a bubbler flask where SnCl<sub>2</sub> was added. The produced Hg<sup>0</sup> was purged using purified N<sub>2</sub> and collected on a gold trap. After 20 min, the trap was transferred to the analytical system where it was connected to an argon gas stream leading to the Cold Vapor Atomic Fluorescence Spectrometry (CVAFS) detector. Collected Hg was desorbed by heating the gold trap.

Samples for analysis of MeHg were distilled to 80% and transferred to a reaction bottle where an ethylating reagent was added (sodium tetraethylborate). The formed ethylated mercury species were purged from the reaction bottle by a N<sub>2</sub> gas stream and collected on Carbotrap adsorbents. The collected mercury species were then thermally desorbed onto a gas chromatography (GC) column. After separation, the organomercury species were

pyrolyzed and detected using CVAFS. A detailed description of the analytical procedures for MeHg can be found in (5).

## RESULTS AND DISCUSSION

### Modeling

The leaching of mercury and MeHg from forest soils were calculated in the GIS-model both before and after the storm to evaluate the increase in leaching due to the storm damage. The results indicate that leaching of mercury to surface waters has the potential to increase significantly in the south of Sweden as an effect of the massive windthrow caused by the storm (Fig. 1). The results suggest that significant increases of methylmercury loadings (>50%) on some lakes may occur and that further monitoring of MeHg levels in water and in fish is warranted.

The leaching coefficients applied in the model calculation are based on measurements of the gross load of mercury to very small streams, hence potential retransformation or retention of mercury has not been considered. The retention effect on mercury and how this affects the behavior of mercury in greater streams and lakes therefore has to be further investigated to fully understand the impact of the mercury load on the sea and surface waters. However, the results can be used to identify areas where the effects of the storm can be severe and where future follow-up of the environmental damage caused by the storm should be carried out.

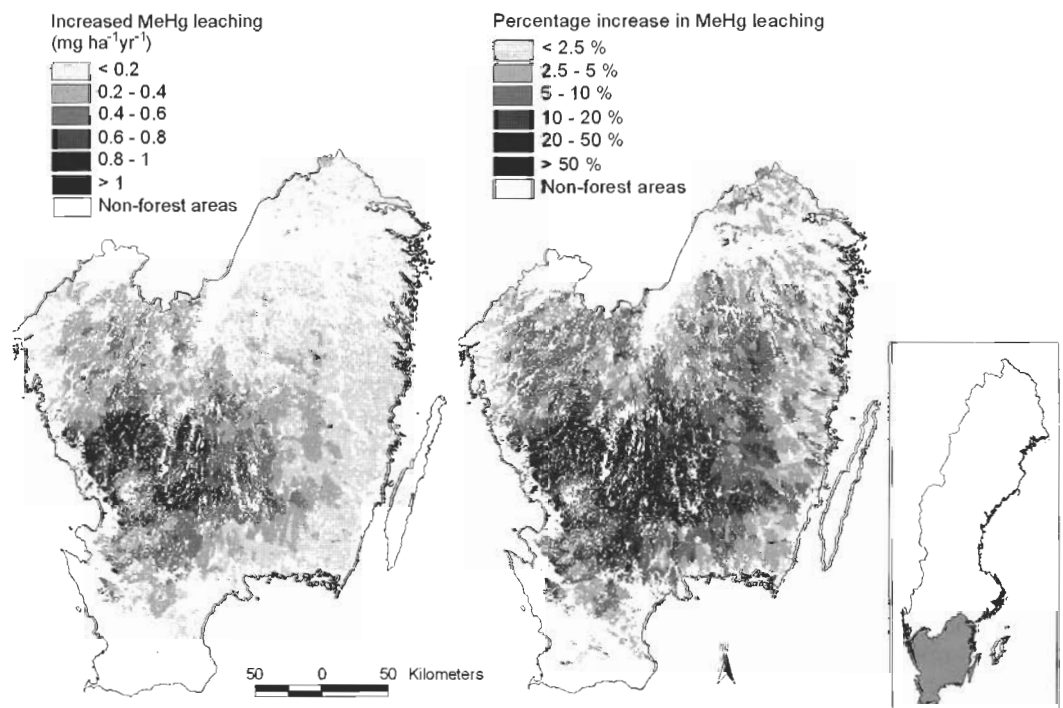
### Measurements

The results of the measurements of mercury in streams located in storm affected areas showed that the level of MeHg increased following the storm. It is therefore likely that increased levels of MeHg already occurred in run-off water from forests during spring 2005. The measurement results (Table 2) suggest that wind throw and logging of storm-felled trees (with associated damage to soils) leads to increase of MeHg leaching in relation to degree of damage.

## DISCUSSION

This study shows that storm-fell events may lead to large increases in MeHg leaching from forests soils to surrounding

**Figure 1. Modeled increased levels of MeHg following the 2005 storm event in SW Sweden (average values during a period of about 5 years).**





**Table 2. Measurements of THg and MeHg in seven catchments affected by the storm in SW Sweden.**

Catchment	THg (ng L <sup>-1</sup> )	MeHg (ng L <sup>-1</sup> )	Degree of damage
Nissan, Ni12	7.9	1	Small
Nissan, Ni2	9.1	1.9	Moderate
Nissan, Ni4	7.5	1.1	Moderate
Nissan, Ni5	5	0.51	Moderate
Nissan, Ni14	14	3.6	Moderate but severe damage to the stream during logging (wheel-tracks)
Nissan, Ni10	15	3.4	Severe
Nissan, Ni13	16	3.3	Severe

waters. The extent of the leaching is mainly related to the damage to the soil caused by forestry machinery in the clearing up operations. The main assumption made in the calculations was that storm-felled areas give an increased MeHg leaching that is of similar dimensions that seen after clear cutting. In clearing up storm-felled forests, measures normally taken to avoid damage to soils and streams may be difficult to take. Thus, it can be assumed that the impacts on MeHg leaching may be even larger than after regular clear-cutting.

To provide further quantitative estimates of the effects of the storm on MeHg leaching, long-term measurements are needed. These should be focused on the areas where large increases were identified in the modeling study described here. Previous studies of MeHg leaching from clear cut catchments have shown that the increase is not temporary but can go on for several years after the event. Thus, long-term monitoring is necessary to be

able to assess the damage and potential risks for fish contamination.

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# Medical Geology: An Opportunity for the Future

## WHY IS GEOLOGY IMPORTANT FOR OUR HEALTH?

Our environment is the entire web of geological and biological interactions that characterize the relationship between life and the planet Earth. Essential and toxic elements in bedrock or soils may become a direct risk for human and animal health and may be the underlying cause of both deficiency and toxicity. Some naturally occurring elements are necessary for our well-being, while others are detrimental to our health. Naturally occurring elements can have detrimental effects on health when ingested in increasing quantities. Metals have always existed and will forever exist, but we cannot avoid the fact that the health of human beings and animals is influenced by metals and other elements in the environment. Geological processes along with human activities of all kinds have redistributed these from sites where they are fairly harmless to places where they adversely affect humans and animals.

Geology may appear far removed from human health. However, rocks are the source of all the naturally occurring chemical elements found on the Earth. Many elements in the right quantities are essential for plant, animal, and human health. Most of these elements enter the human body via food and water in the diet and through the air that we breathe. Through the weathering processes, rocks break down to form soils on which crops and animals that constitute the food supply are raised. Drinking water moves through rocks and soils as part of the hydrological cycle. Much of the dust and some of the gases present in the atmosphere are the result of geological processes. Hence, a direct link exists between geochemistry and health due to ingestion and inhalation of chemical elements.

Volcanism and related igneous activities are the principal processes that bring elements to the surface from deep inside the Earth. For example, the volcano Pinatubo ejected in just over 2 d in June 1991, about 10 billion tonnes of magma and 20 million tonnes of SO<sub>2</sub> and the resulting aerosols influenced the global climate for 3 y. This event alone introduced 800 000 tonnes of zinc, 600 000 tonnes of copper, and 1000 tonnes of cadmium to the surface environment. In addition to this, 30 000 tonnes of nickel, 550 000 tonnes of chromium, and 800 tonnes of mercury were also added to the Earth's surface environment. Volcanic eruptions redistribute some of the harmful elements, such as arsenic, beryllium, cadmium, mercury, lead, radon, and uranium, plus most of the remaining elements, many of which may have still undetermined biological effects. It is also important to realize that there are on average 60 subaerial volcanoes erupting on the surface of the Earth at any given time, releasing various elements into the environment. Submarine volcanism is even more significant than that at continental margins, and it has been conservatively estimated that there are at least 3000 vent fields on the midocean ridges (1). One interesting fact is that about 50% of SO<sub>2</sub> is of natural origin, mainly from volcanoes, and the other 50% is from human sources.

The naturally occurring elements are not distributed evenly across the surface of the Earth, and problems can arise when element abundances are too low (deficiency) or too high (toxicity). The inability of the environment to provide the correct chemical balance can lead to serious health problems. The links between environment and health are particularly important for subsistence populations that are heavily depen-

dent on the local environment for their food supply. Approximately 25 of the naturally occurring elements are known to be essential to plant and animal life in trace amounts, including Ca, Mg, Fe, Co, Cu, Zn, P, N, S, Se, I, and Mo. On the other hand, an excess of these elements can cause toxicity problems. Some elements such as As, Cd, Pb, Hg, and Al have no or limited biological function and are generally toxic to humans.

Many of these elements are known as trace elements because they generally occur in minute ( $\mu\text{g kg}^{-1}$  or ppm) concentrations in most soils. Trace element deficiencies in crops and animals are therefore commonplace over large areas of the world, and mineral supplementation programs are widely practiced in agriculture. Trace element deficiencies generally lead to poor crop and animal growth and to reproductive disorders in animals. These problems often have the greatest impact on poor populations who can least afford nutritional interventions for their animals.

## WHY IS THE INTEREST IN MEDICAL GEOLOGY INCREASING?

Certainly, for the past several decades there has been a growing awareness of environmental health issues (2). More and more people in developed and developing countries are becoming aware of the potential health impacts of environmental pollution. By and large these concerns had been focused on industrial contamination. However, there has long been a small but active group of researchers who recognized that natural materials and processes could be as dangerous as the pollution from anthropogenic materials and processes. Perhaps the success in improving air and water quality in many developed countries has given us confidence that we can now tackle nature and mitigate or eliminate the environmental health issues caused by exposure to natural materials (3, 4, 5).

Although geologic factors play key roles in a range of environmental health issues that impact the health and well-being of billions of people worldwide (6), there is a general lack of understanding of the importance of these factors on animal and human health among the general public, the biomedical/public health community, and even within the geoscience community. To assist on improving our understanding of those factors of common interest to the geoscience and biomedical fields, in 1996 the International Union of Geological Sciences (IUGS) commission Cogeoenvironment established an international working group on medical geology led by Olle Selinus of the Geological Survey of Sweden (SGU). The primary aim of the medical geology working group was to increase the awareness of this issue among geoscientists, medical specialists, and the general public. In 2000, a new project was subsequently established by the United Nations Educational, Scientific, and Cultural Organization. The primary aim of the projects were to bring together, at the global scale, scientists working in this field in developing countries with their colleagues in other parts of the world. The International Council of Scientific Unions (ICSU) also sponsored international short courses in this subject, a cooperation involving the SGU, US Geological Survey (USGS), and the US Armed Forces of Pathology (AFIP). In 2006, as a result of the remarkable growth on

medical geology issues, a new association was established: the International Medical Geology Association (IMGA) (6, 7, 8).

We believe that the internet has also played a major role in the resurgence of medical geology. The internet has provided the ability to instantly disseminate information to every corner of the world. Graphic color images, announcement of upcoming conferences and new books, publication of research reports, etc. now are within the reach of every person concerned with these issues even in the most remote parts of the planet. An indication of the power of the internet and the rapid growth of medical geology can be seen from the number of medical geology "hits." As of October 2006 "medical geology" produced more than 40 000 hits on the Google search engine, while just a few years ago the hits were measured in the hundreds.

### SHORT COURSES: SPREADING THE MESSAGE

With the support of IUGS, USGS, AFIP, SGU, and the host countries, the ICSU money was used to fund many more short courses than had been proposed. These courses have been presented in 30 countries and have been attended by more than one thousand students and professionals with backgrounds in geoscience, biomedical/public health science, environmental science, pathology, geography, engineering, chemistry, etc. The leaders of the short course are Jose Centeno, Bob Finkelman, and Olle Selinus. In addition, local scientists are invited to describe medical geology work going on in their regions, and in some courses students have been encouraged to present their work on medical geology in the form of posters and special papers.

The aim of the short courses is to share the most recent information on the relationship between toxic metal ions, trace elements, minerals, etc. and their impact on the environmental and public health issues. The scientific topics of the course include environmental toxicology; environmental pathology; geochemistry; geoenvironmental epidemiology; extent, patterns, and consequences of exposures to toxic metal ions; and analysis of geologic and biologic materials.

The courses, generally 2 to 3 days in length, are intended for anyone interested in the effects of natural materials and natural geological events on animal and human health. An important objective of the courses is to provide an opportunity for forming contacts and networks between professionals working in different countries and on different aspects of environmental health issues. We have produced a 300 page syllabus and a CD containing the lecture materials used in the short course, as well as supplementary material such as reprints of relevant articles for participants to use in their regions and on their respective disciplines. The use of this course material by participants and students has been highly encouraged, as has the preparation of lectures and other didactic materials.

### EDUCATION

The biggest challenge facing medical geology is the integration of geoscience and biomedical public health research, including the availability of funds to conduct research and training activities. The researchers attend separate conferences, subscribe to different journals, and to some degree have different philosophical approaches and speak different languages. A concerted effort by these two communities will bring medical geology to its full potential. Biomedical/public health organizations have demonstrated interest equal to that of the geoscience community. In addition, universities, medical schools, research hospitals, and biomedical professional organizations in different countries have all shown interest in this field, as have chemists, engineers, environmentalists, geographers, etc. (9, 10, 11).

Several books on medical geology have been published in the past few years (12). In 2002 Catherine Skinner and Tony Berger edited *Geology and Health*, the proceedings of a medical geology conference that was held a few years earlier in Uppsala, Sweden (13).

In 2005 Elsevier published *Essentials of Medical Geology* edited by Olle Selinus and six associate editors: Brian Alloway, Jose Centeno, Bob Finkelman, Ron Fuge, Ulf Lindh, and Pauline Smedley. *Essentials of Medical Geology* is composed of scientific contributions from over 60 authors around the world. About 50% are geoscientists and about 50% are physicians, veterinarians, and other scientists (14).

As a book dedicated to the emerging field, *Essentials of Medical Geology* was in November 2005 recognized as a "Highly Commended" title in the public health category by the British Medical Association, one of the most prestigious medical associations in the world. The book is one of the best of all published books in public health in 2005. They bestow awards upon publications "which are deemed to best fulfill the criteria of clinical accuracy and currency and which maintain a high standard of design and production." *Essentials of Medical Geology* was also awarded a second prestigious reward in January 2006. It was one of two winners in the "Geology/Geography" category of the 2005 Awards for Excellence in Professional and Scholarly Publishing. The PSP awards recognize both editorial standards as well as design and production standards. PSP is the Professional Scholar Publishing division of the Association of American Publishers. The book has now thus been recognized in both communities for which it was intended (first by the British Medical Association, and then as a geology resource).

Colleges and universities in several countries (Sweden, Egypt, the United States) have begun to offer credit courses in medical geology using the book *Essentials of Medical Geology*. Students in many countries have expressed interest in attending such courses and even in majoring in medical geology. Scores of graduate students in many countries are currently working on a wide range of medical geology issues, and students are working on medical geology issues for masters and doctorates in several countries including Turkey, Sweden, the United States, Russia, China, and elsewhere. Research Fellowships and postdoctoral studies in medical geology have been offered by the US Armed Forces Institute of Pathology, the US Geological Survey, and the US Department of State.

The Armed Forces Institute of Pathology has also created a medical geology registry that contains information, diagnoses, and tissue and body fluid samples on a range of health problems caused by environmental and natural geologic materials.

These examples are all solid and necessary indications of a very healthy, growing interest in the subject of medical geology.

### INTERNATIONAL IMPACT

Interest in medical geology has been demonstrated in virtually every country (15). During the past few years, scientific organizations in Argentina, Australia, Brazil, Canada, China, Chile, Egypt, Great Britain, India, Ireland, Hungary, Japan, Lithuania, Malaysia, Mexico, Monaco, New Zealand, Romania, Russia, South Africa, Sweden, Turkey, the United States, Uruguay, Venezuela, and Zambia have sponsored one or more medical geology short courses. In many of these countries multiple organizations have sponsored the courses, and many of these organizations have provided financial or logistical support to ensure their success. Similar courses have been requested by organizations in Cyprus, Nigeria, Portugal, Italy, Kenya, Tanzania, Pakistan, Thailand, Taiwan, and Indonesia. Organizations and individuals around the world are taking initiatives to



Figure 1. International Medical Geology Association.

develop medical geology programs and activities. This is particularly the case in Brazil, Turkey, Australia, Canada, Eastern Africa (Kenya and Tanzania), and South Africa, and Russia.

Other national and international organizations have created committees or divisions dedicated to medical geology. The latest is the Geological Society of America, which, at its annual meeting in the fall of 2005, created the Geology and Health Division. During the past 5 y there have been at least six technical sessions and symposia devoted to medical geology at the Geological Society of America annual meeting and regional meetings and dozens of similar sessions at local, regional, and international meetings around the world. Medical geology sessions have been organized at major medical and pathology conferences including the International Academy of Pathology, the International Symposium on Metal Ions in Biology and Medicine, and the US Annual Force Health Protection Conference.

### INTERNATIONAL MEDICAL GEOLOGY ASSOCIATION (IMGA)

To respond to the needs of this growing discipline, a new association has been created, the International Medical Geology Association (IMGA) (Fig. 1). The Association was originally launched in Florence in 2004 at the 32nd International Geologic Congress. Since its creation, the association has attracted over 1000 corresponding members from about 70 countries. To better serve the regional needs of our members, regional divisions on medical geology are being formed in South America, Southern Mediterranean, Asian subcontinent, sub-Saharan Africa, North America, etc. A dynamic website ([www.medicalgeology.org](http://www.medicalgeology.org)) has been created containing information on current activities in medical geology. Current and past issues of the organizational newsletter can be downloaded from the site.

The IMGA will also have regional councillors who will represent IMGA in different parts of the world. We have appointed six councillors to represent the broad geographic distribution of medical geology and the wide range of disciplines that are embraced by this topic. Current regional councillors are listed on the website.

Medical geology regional divisions shall also be formed to encourage broad participation in medical geology research, training, and education and to disseminate medical geology information in their respective regions.

### INTERNATIONAL YEAR OF PLANET EARTH

The ultimate example of organizational support may be the United Nation's proclamation in December of "The International Year of Planet Earth." The initiative will seek to raise the awareness and role of the Earth sciences in society in the minds of politicians, decision-makers, the media, and the general public. A significant component of this important initiative will

be promoting awareness, providing education, and supporting research on a medical geology theme referred to as Earth and Health.

The specific aim of the International Year of Planet Earth is to demonstrate new and exciting ways in which Earth sciences can help future generations meet the challenges involved in ensuring a safer and more prosperous world.

The achievement of this aim will be supported by two major programs

- (i) Outreach Program including educational ventures at all levels
- (ii) Science Program concentrating on "big issues" of complex interaction within the Earth system and its long-term sustainability.

Medical geology will thus be one of the ten topics within the Year of Planet Earth. The year will be a triennium between 2007 and 2009. Medical geology is also one of the five topics within the GeoUnion initiative.

### AN OPPORTUNITY FOR THE FUTURE

It is always risky to attempt to predict what the future holds. However, we are confident that the future for medical geology looks promising. The book, *Essentials of Medical Geology*, has received an overwhelmingly positive response. The reviews have been uniformly positive, and the first printing has nearly sold out in less than a year. The book will stimulate the teaching of medical geology in colleges and universities. The medical geology short courses will continue to attract enthusiastic medical geologists and future students. The International Medical Geology Association should provide a stable platform for the exchange of ideas and dissemination of information. The International Year of Planet Earth will be of great importance not only concerning outreach but also in funding medical geology research all over the world. The wide range of other medical geology activities enumerated above should maintain enthusiasm and momentum for the next few years. Medical geologists are at the forefront to demonstrate that what we have to offer will indeed benefit society by helping to improve the quality of life for people around the world.

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