Issues in Toxicology

Alan B. G. Lansdown

The Carcinogenicity of Metals

Human Risk Through Occupational and Environmental Exposure

RSC Publishing

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I should like to dedicate this publication to my grandchildren, Emma, Rosie, Molly, Caroline and Christopher. Whatever aspirations they may develop in the future, I hope that their endeavours will bring personal rewards and satisfaction as have come my way in the study of metals over more than 40 years.

This volume is also dedicated to my wife, Veronica, who has given me loving support and friendship throughout my endeavours.

I acknowledge with sincere gratitude the fruitful conversations and constructive criticism provided by many friends and acquaintances at the former Charing Cross and Westminster Medical School, Birkbeck College and the British Industrial Biological Research Association.

Foreword

The ancient Egyptians had knowledge of the dangers of antimony, copper, crude arsenic and lead, and, in a number of cultures in the last three millennia, minerals have been used as poisons. A more clearly defined role for the widespread effects of these elements on human health and in disease states has been identified and characterised during the last two centuries. Initially, the need for a particular element was often discovered by observations of deficiency states in particular locations (iodine for goitre, as an example) but as a wider interest in comparative epidemiology developed, conditions induced by large local excesses of particular minerals were also identified and could be attributed to the effects of this excess (arsenic in drinking water in central Europe, say). Observations relating to the effects of therapeutic interventions had also shown that mercury and its salts, gold and silver, all used in manner that was hoped to confer benefit, may all cause evident human toxicity.

That we need many minerals in varying amounts is clear for reasons set out in early chapters of this book. As with vitamins, it is also clear that an excessive intake can be harmful – and that acute and chronic toxicity may result from exposure to excessive intake. These exposures may occur for a number of reasons and from varied sources, many of which have been recognised in comparatively recent times.

Occupational disease (wrist drop in painters) was recognised as a marker of toxic exposure and helped to define the cause of the toxic effects seen. In a clear historical example, mining of uranium-bearing ore in Schneeberg (Germany) and Jachimov (Czechoslovakia) both for metals and the manufacture of uranium dyes had been carried out for centuries and was known to be associated with lung disease – both pulmonary fibrosis and carcinoma of the lung, although this distinction was not evident to contemporary observers when the link was published in 1879. The development of industry and of industrial processes together with the gradual development of health care relating to those

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working in industry and better record keeping relating to workers and the local environment (an often undervalued element in identifying causality in disease processes) made clear that industrial development has produced well-defined problems such as the presence of organic mercury compounds in effluvia (Minamata Bay).

Associations of a different kind, relating to long-term exposures and to exposures to levels of toxin that did not produce acute illness or evident direct toxicity, were harder to identify. Although potentially carcinogenic actions of minerals were often investigated after singular associations between occupations and uncommon tumours had been identified, modern methods of diagnosis and record keeping were needed to provide the means to question potential causality between exposures and common tumours. These associations would often promote a search for pathogenetic mechanisms by experimentation.

Epidemiological research is a valuable weapon in identifying apparently causative factors in disease. Although causes may be defined in a number of ways, in pragmatic terms it is clear that if the elimination of a causal factor results in a change in disease incidence, its relevance to public health is evident. This is what epidemiological research has sought to achieve in the field of exposure to minerals examined in this book. But the epidemiological approach has its dangers and before constructing a hypothesis, it should be remembered that the strength of any association, consistency of results in different studies and consistent experimental evidence are the most powerful discriminants in examining links. Experimental work must be constructed around a hypothesis of action that is clearly defined for it to be capable of translation between species, say.

This book is a comprehensive survey of a major health concern (carcinogenesis) relating to the use of minerals. It considers all those elements about which human health concerns have been thought to exist, having defined a view of carcinogenicity that is internationally adopted in regulatory circles and which is clearly set out in initial chapters.

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Preface

Metals have played a decisive role in the development of human civilisations from earliest times. They have shaped developments in engineering, science and medicine and in the past century many Nobel Laureates were founded on research using metals. Marie Curie focussed her early research on the magnetic properties of steel but was later to perform fundamental research into the radioactivity of metals and the properties of uranium. Paul Ehrlich made notable contributions to the understanding of cancer and introduced the arsenic-related therapy Salvarsan as one of the first effective cures for syphilis and other infections prevalent at the time. Countless other memorable contributions could be included, but whilst we accept the value of metals and metalloid elements in industry and medicine, since the 1950s at least, clinicians, environmentalists and toxicologists have become aware that few substances in daily use or to which humans are exposed in daily life or in occupational environments and in medicine are entirely safe, and that a modicum of risk arises through excessive exposure, abuse or accident.

The present review re-evaluates epidemiological and occupational health studies, experimental studies in animals and *in vitro* experiments relating to the toxicity of metal and metalloid elements for which evidence of carcinogenicity has been presented. Human carcinogenic risk is substantiated in relation to arsenic, beryllium, thorium, chromium, radioactive elements, probably lead, and some nickel and cobalt compounds, and respirable silica particles, but the carcinogenicity of iron, aluminium, titanium, tungsten, antimony, bismuth, mercury, *cis*-platin, precious metals, and certain related compounds in humans is unresolved. The toxicity and carcinogenicity of each element is specific but correlates poorly with its position in the Periodic Table. Carcinogenicity differs according to the valency of the ion and its ability to interact with and penetrate membranes in target cells and to bind, denature or induce mutations by genotoxic or epigenetic mechanisms. The influence of lifestyle, environmental

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contaminants and human factors in the interpretation of epidemiological studies is discussed. Further studies are indicated to investigate the interaction between xenobiotic elements and genotype as an explanation for regional variations in population response. The relevance of experimental studies in isolation in predicting human risk through metal exposures is questioned. *In vitro* studies in mammalian cell lines and bacterial reversion tests provide evidence that certain metals and metalloid elements are capable of inducing mutagenic and clastogenic changes, but they provide limited information on target organ susceptibility, inherent protective mechanisms within the intact body or immunomodulation.

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CHAPTER 1

Introduction

1.1 Introduction

Metals and metalloid elements are ubiquitous in the human environment (Figure 1.1). They are present to a varying extent in the rocks and soils throughout the world and exist in the air we breathe and in our food or drinking water. Natural deposits in some parts of the world are extensive and in the case of lead and arsenic are prominent sources of local health problems.[1,2] Inland waterways, estuaries and open sea contain the largest natural sources of metals and their compounds. In addition, these waters accumulate metal residues eluted from inland sources, pesticides and agrochemicals, factory wastes and sludges, deposits from landfill sites and even domestic waste. Metal residues enter local streams, lakes and rivers to be disseminated into open water through tides, offshore currents and adverse weather conditions. This is well illustrated by discharges of silver residues into the San Fransisco Bay area in California (the so-called Great Silver Estuary) where sediments in one year were as high as 8800 kg.[3] Other notable examples include the Minamata Bay catastrophe in Japan in 1953 where an estimated 27 tons of mercury compounds were discharged into sea waters,[4] and local disasters following release of cadmium residues into rivers by mining companies (Figure 1.2).[5,6] In such cases, cadmium is concentrated in local food sources such that fish in the rivers start to die and rice irrigated with river water fails to grow. Cadmium poisoning is related to the human disease Itai-Itai, which causes softening of the bones and kidney failure.[7,8] Cadmium and cadmium compounds are now listed as human carcinogens.[9,10] Sea water possibly contains all stable and some radioactive metal and metalloid elements listed in the Periodic Table, albeit some being present in minute quantities.

Ecologists, environmentalists and regulatory toxicologists throughout the world are justifiably concerned that high concentrations of toxic metals discharged into sea water concentrate in marine deposits, fish and marine life and

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Figure 1.1 Metals and metalloid elements in the human environment. Soils in the Vetagrande region of Zacateras in Mexico are rich in lead, mercury, silver, gold, zinc and copper.
(With kind permission of Dr JOSÉ RODRÍGUEZ, of the Fundación Universitaria Iberoamercana, Mexico.)

Figure 1.2 Human contamination through food chains. Firefighters pour polyaluminium chloride into a pool to dilute the cadmium-polluted water in the Longjiang river in China.
(Photo: AFP/Getty Images.)

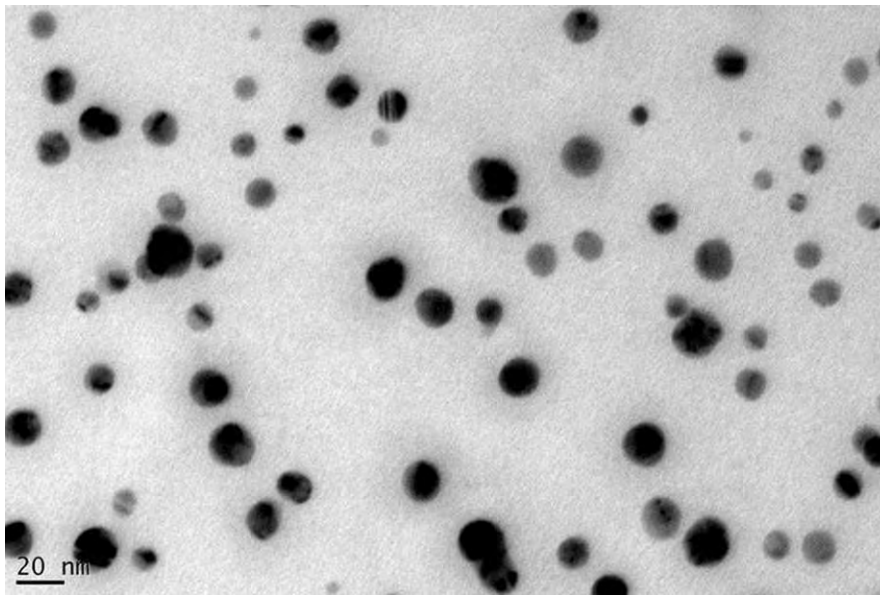

Figure 1.3 Nanoparticles of metallic silver <20 nm diameter. The high surface to volume ratio increases their capacity for ionisation and changes physico-chemical properties: the grain boundary phenomenon.
(By courtesy of Dr S. Misra, Natural History Museum, London.)

enter human food chains. Other major ecological and human health concerns relate to the discharge of metal particles into the air by volcanic action, natural erosion of rocks and shales, emissions and effluents from mining, extraction and refining from metal industries, and incineration of commercial and domestic waste. Plants and food animals in contaminated pastures accumulate lead, mercury, cadmium and other xenobiotic elements. Other concerns relate to the increasing use of nanotechnology and the production of minute metal particles of 20 nm or less for commercial purposes.[11–13] Nanoparticles in the air present special problems. They are considered to have different surface properties, and the physico-chemical properties of their grain boundaries may be more injurious to health.[14] Nanoparticles of silver are probably more than 100-fold more soluble than silver foil or filings.[15] Special health problems of pulmonary fibrosis, pneumoconiosis, chronic respiratory disease and even cancer are recognised following inhalation of industrial dust and nanoparticles of respirable size of gold, silver, chromium, silica and nickel in industrial environments (Figure 1.3).

1.2 Metals as Nutrients

The human body has evolved over many millennia to depend upon certain metals and metalloid elements as constituents of cellular structure or intercellular matrices, electrolytes, or as components or co-factors of key enzyme

Table 1.1 Metal and metalloid ions as nutrients in the human body.

Element	*Total body concentration (g)*	*Concentration in circulation*	*Recommended daily intake*	*Daily excretion*
Calcium	1500	8.8–10.5 mg dL^{-1}	800 mg	100–350 mg
Chromium	0.05–0.10	0.5–5.0 μg L^{-1}	5–100 μg	5–10 μg L^{-1}
Cobalt	0.0015	<1 μg/L	1–5 μg vit. B_{12}	<1μg/L
Copper	0.1–15	80–153 mg dL^{-1}	2–5 mg	10–30 μg
Iron	4–4.5	4000 mg	10–14 mg	<100 μg
Magnesium	25	1.4–2.4 mg dL^{-1}	350 mg	75–150 μg
Manganese	10–20 μg	1–200 μg L^{-1}	1–8 mg	0.1–1.2 μg
Molybdenum	0.009	30–700 nmol L^{-1}	0.5–2.0 mg	22–173 μg
Nickel	0.10	3–8 μg L^{-1}	300–900 μg	10–100 μg L^{-1}
Potassium	180	3.5–5.0 mmol L^{-1}	2500 mg	66–85 mmol[a]
Selenium	0.013	1.3–4.3 μmol L^{-1}	60 μg	17 nmol
Silicon	0.024	1000–5000 μg L^{-1}	10 000–50 000 μg	15 000 μg L^{-1}
Sodium	64	135–145 mmol L^{-1}	2500 mg	129–181 mmol[a]
Strontium	3.5–4 mmol	12 μ L^{-1}	1–3 mg	144 μg L^{-1}
Tin	0.017	140 μg L^{-1}	3.5–17 mg	10–20 μg L^{-1}
Vanadium	0.018	10 μg L^{-1}	25 μg	<10 μg L^{-1}
Zinc	1–2	80–110 μg dL^{-1}	7–17 mg	0.4–0.6 mg

[a]Urinary levels vary according to sex and levels of salt intake.

systems or biosynthetic pathways (Table 1.1).[16–19] Metalloenzymes containing calcium, magnesium, zinc, iron and copper are important at critical stages of the cell cycle and may have a role in carcinogenic transformation. Patterns of uptake, metabolism, metal-binding proteins, cellular metabolism and excretion are well defined for all nutrients, although optimal levels for good health for minor trace metals such as molybdenum, vanadium, chromium and nickel are still debatable. The roles of blood concentrations, hormones or other factors regulating uptake, levels in the systemic circulation, tissue accumulation and excretion are imperfectly understood.

Macro- and trace nutrients are defined broadly as substances required at appropriate concentrations for optimal health and wellbeing. Demands for different nutrients vary according to age, sex and physiological state (especially pregnancy and lactation). The body displays characteristic signs of metal ion deficiency through malnutrition, dietary imbalances and malabsorption syndromes, through genetic or acquired disease processes. These conditions regress when deficiencies are corrected, as illustrated by iron deficiency anaemia (IDA), hypozincaemia, hypocalcaemia and cobalt deficiency (manifest through suboptimal Vitamin B_{12} levels).[20–24] The role of tin and strontium as trace metal nutrients is still unclear.

Metal ions interact in the body and ionic balances determined by carrier proteins, are critical in regulating the programmed sequence of proliferation in stem cells, maintenance of cellular architecture, cell-to-cell adhesion and functional differentiation.[25–28] Calcium, for example, interacts with zinc, magnesium, copper and iron and imbalances in metal-to-metal ionic ratios can

be detrimental at specific phases in the cell cycle and in the post-mitotic functional differentiation in tissues such as skin, bone, bone marrow and gastrointestinal mucosae with high stem cell populations.[29] Calcium is a particularly important macro-nutrient and more than 70 calcium-binding proteins are present in the body, notably the so-called ''EF-hand proteins'', cahederins, calmodulin and S-100 proteins. Most display binding sites for other metal ions, notably strontium, lead, aluminium and mercury.[30,31] Strontium mimics calcium and can substitute for it in biological systems, particularly musculoskeletal tissues.

Elements such as silver, arsenic, aluminium, bismuth, platinum and lead have no nutritional function but are present occasionally in the body at low levels (Table 1.2). Several bind to proteins such as metallothioneins, ferritin, calmodulin, *etc*. and can impair the availability of essential nutrients if present to excess (Table 1.3). Arsenic accumulates in bone and displaces calcium from hydroxyapatite binding; clinical studies in Bangladesh and elsewhere have shown that arsenic in drinking water is a cause of retarded body growth and brittle bones.[32] Other xenobiotic elements such as lead, cadmium, mercury and antimony are also cumulative poisons which deposit in liver, neurological tissues, kidney and bone with potential toxicological effects.

The human body exhibits a variety of inherent protective mechanisms against the toxic effects of excesses and imbalances in nutrient metal or

Table 1.2 Xenobiotic metal and metalloid elements present in the human body.

Aluminium	Antimony
Barium	Bismuth
Gold	Mercury
Silver	Tungsten (Wolfram)
Zirconium	Arsenic
Beryllium	Cadmium
Lead	Platinum[a]
Titanium	

[a]Platinum-group metals include palladium, rhodium, ruthenium, iridium, and osmium which commonly occur together in nature.

Table 1.3 Metallothionein and metal-binding in human tissue.

Metallothionein	*Expression*	*Metal induction and binding*
I	Epithelia	Zn, Cu, Cd, Hg, Ag, Au, As, Pt
II	Epithelia	Zn, Cu, Cd, Hg, Ag, Au, As, Pt
III	Brain	Zn, Cu, Cd
IV	Squamous epithelia, tongue	Zn, Cu, Cd, Co

metalloid ions, as well as uptake of xenobiotic ions by ingestion, inhalation or percutaneous absorption. The main protective mechanisms seen include:

- Gastrointestinal physiology and factors that modulate metal ion absorption
- Intestinal commensal bacteria that detoxify, oxidise or reduce metal or metalloid ions
- Dietary factors such as phytate, plant fibres and organic matter that bind metal ions
- Epidermal cytokeratins that strongly bind metal cations, thereby controlling percutaneous absorption
- Intra- and inter-cellular metal binding proteins that chelate or otherwise bind xenobiotic ions or modulate their uptake and metabolism
- Pulmonary alveolar macrophages that phagocytose and "mop-up" inhaled particles
- Selective uptake and competitive receptor binding on cell membranes
- Metal-binding proteins.

Metal-binding proteins including calmodulin, calbindin, caeruloplasmin and the cysteine-rich metallothioneins (MT) serve critical functions as cytoprotective agents. The MT are induced by and play an instrumental role in the metabolism of key nutrients such as zinc, copper and selenium, but they strongly bind ions including arsenic, bismuth, cadmium, gold, silver and mercury. Transferrin is a key iron-binding protein, but this multivalent molecule also binds bismuth, aluminium, indium, vanadium and gallium, any of which, if present to excess, disturb iron metabolism.

The majority of metal and metalloid elements are toxic to some extent in humans. At least 12 are carcinogenic under some circumstances. Toxicity and carcinogenicity can occur under a variety of conditions but, mining, refining, heavy metal industries and exposure through contaminated drinking water are major sources of exposure. Whereas haematite ore is relatively harmless, mining of the ore in many parts of the world presents risks of lung and other cancers through inhalation of the radioactive gas radon.[33] A second example is seen with gold mining. Gold is not carcinogenic but miners exposed to arsenic are exposed to lung cancer.[34]

1.3 Diagnosis of Carcinogenicity

The US National Toxicology Programme (NTP), US Environmental Protection Agency (EPA), US Department of Health and Human Services (DHHS), International Agency for Research on Cancer (IARC) and World Health Organization (WHO) have reviewed published work over the past 100 years and, on the basis of collated observations from epidemiological studies, case reports and experimental studies in laboratory animals, have classified known carcinogenic materials in five main categories (Table 1.4).[9,35–39] Authoritative guidance on the carcinogenicity of metals and other environmental

Table 1.4 IARC Classification of Carcinogens (IARC, 2006).

Category	*Designation*	*Classification*
Group 1	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans. Exceptionally, where there is insufficient evidence for carcinogenicity in humans but there is sufficient evidence in experimental animals and strong evidence the agent acts through a relevant mechanism of carcinogenicity
Group 2	Category contains agents for which the degree of evidence for carcinogenicity in humans is almost sufficient, or where there are no human data but for which there is evidence of carcinogenicity in animals	
Group 2A	Probably carcinogenic to humans	Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Alternatively, where inadequate evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals and strong evidence that carcinogenesis is mediated by a mechanism that operates in humans
Group 2B	Possibly carcinogenic to humans	Agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals
Group 3	Not classified as carcinogenic to humans	Inadequate evidence for carcinogenicity in humans and inadequate or limited evidence of carcinogenicity in experimental animals. Agents showing strong evidence that mechanisms of carcinogenicity in experimental animals do not operate in humans. Not a determination of non-carcinogenicity but may indicate that more research is needed
Group 4	Probably not carcinogenic in humans	Evidence suggesting a lack of carcinogenicity in humans and experimental animals.

contaminants is contained within the 12 Reports on Carcinogenicity (RoC), monographs of IARC working parties and numerous authoritative independent reviews.[106]

A ''cancer hazard'' is defined by the IARC in their Preamble to the *Monographs*,[106] as:

a. An ''agent'' capable of causing malignant neoplasms in one or more organ systems under some circumstances
b. An agent or related compound capable of ''increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity''.[10,36]

A ''cancer risk'' is an estimate of the carcinogenic effects expected through occupational or environmental exposure to a carcinogenic agent. Where an agent is shown to induce an increased incidence of benign neoplasms, this may be taken into account in judgements of carcinogenicity. The terms ''neoplasm'' and ''tumour'' are used interchangeably. The IARC Expert Working Parties classify the term ''agents'' broadly to include individual elements and related compounds, complex mixtures, occupational exposures, lifestyle factors and other potentially carcinogenic exposures. The classification of carcinogenic agents is updated regularly as newer information comes to hand.

Scientific judgement as to whether exposure to an element, chemical compound, mining or extraction process or finished product constitutes a proven or anticipated human carcinogenic risk depends upon a balanced, scientific and statistically valid assessment of:

- Occupational and environmental health reports, human case and forensic studies
- Regulatory style experimental studies in animals
- Short-term laboratory *in vitro* tests to demonstrate: mutagenicity, DNA damage, cell transformation, clastogenicity, genotoxicity and molecular toxicity.[39–47]

The RoC have documented certain agents as ''reasonably carcinogenic to humans'' on the basis of their being ''structurally related to a class of substances whose members are listed as carcinogens or are reasonably anticipated to be human carcinogens''. In all, conclusions are based on a consideration of all relevant information. ''This is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects or other data relating to mechanisms of action or factors that may be unique for a given substance.''[9]

1.4 Mechanisms of Carcinogenicity as Applied to Metals and Metalloid Elements

The scientific community has moved on far beyond the initial concepts of chemical carcinogenesis, founded on the studies of Isaac Berenblum and Phillip Shubic in the 1940s, that chemical carcinogenesis involves at least two stages – induction and promotion.[48] Recent advances in molecular genetics dictate that, these days, greater emphasis should be placed on mechanism-based carcinogenesis and the action of xenobiotics on cellular growth, mitotic homeostasis and the activation and expression of oncogenes.[9,42,49–52]

Early concepts of multi-step chemical carcinogenesis envisaged an initial (induction) phase involving DNA damage, chromosomal change, impairment of DNA replication and repair followed by one or more promotional phases in which this pre-neoplastic state is promoted to frank tumour formation.[53–61] Promoters such as croton oil may have marginal or no carcinogenic activity but

serve as mitogens, motivating transformed cells to colony formation and metastasis. Phorbolester A_1, isolated from croton oil, was shown to invoke increased permeability in nuclear membranes preceding excitation of DNA synthesis and nuclear enlargement. Other non-carcinogenic promoters include non-specific stress factors such as noise, disturbances in diurnal rhythms, dietary factors, infection, immuno-suppression and oxidative stress. Complete carcinogens are defined as substances capable of inducing irreversible mutagenic changes in target cells with or without metabolic transformation, followed by transformation/promotion of stem cells to tumour formation.[53]

Biochemical and molecular evidence emphasises that elements such as arsenic, cadmium, chromium (VI), cobalt and nickel compounds can evoke carcinogenic changes through mechanisms other than direct genotoxicity, DNA binding or chromosomal aberrations.[62] These so-called "*epigenetic changes*", cumulatively leading to altered signal transduction, regulation in gene expression and carcinogenesis, include chronic inflammation, immunosuppression, oxidative change and induction of reactive oxygen species, changes in DNA-methylation patterns and activation of hormonal receptors.[63,64] Growth factors, cytokines and other subcellular or intracellular factors are probably involved. Epigenetics is a new and challenging aspect of carcinogenesis and is well illustrated by studies in molecular genetics of unequivocal carcinogens such as arsenic.[51] Plausible studies now suggest that epigenetics should be defined as a "*study of heritable changes in gene function that occur without any direct changes in DNA sequence*". Epigenetic effects influence gene expression and regulatory mechanisms controlling tissue-specific cellular receptors, signal transducers and effector molecules.[65]

Alterations in DNA-methylation patterns probably constitute a significant part of the carcinogenic process and involve transcriptional inactivation or activation of cancer-related genes.[51] Molecular studies with arsenic emphasise that carcinogenesis is principally a "*disease of stem cells*" which express a range of cell surface markers responsive to stem-cell maintenance-related genes.[66] They may also involve covalent modifications in the amino acid residues in histones around which DNA is wrapped.[67–69] Changes in the methylation status of cytosine bases in cytosine–phosphate–guanine dinucleotides (*i.e.* CpG islands) within the DNA molecule act in a form of gene "silencing". Grønbaek viewed cancer developing when "*cells acquire specific growth advantages through a stepwise accumulation of heritable changes in gene function*" modulated by tumour suppressor genes that inhibit cell growth and oncogenes that promote cell growth and survival.[69]

1.5 Epidemiological Evidence

Numerous epidemiological studies are published claiming to demonstrate that exposure to metal or metalloid elements in industrial environments or through contamination of food, drink or air is a cause of human cancer. Few are scientifically sound and many fail to demonstrate a clear correlation between exposure to metal/metalloid and evidence of tumour induction/promotion.[70–75]

Observer bias is evident in some older studies but long lag phases of 20 years or more years between presumed exposure and evidence of tumours (*e.g.* arsenic, lead and cadmium), failure adequately to allow for human lifestyle factors, and incomplete reporting complicate the true evaluation of risk in many epidemiological studies.[76–78] Few industrial environments, mining, smelting and refining operations contain a single toxic element, and in the case of electroplating, steel production, the electronics industry, and waste metal recycling, workers are exposed to several toxic and potentially carcinogenic materials capable of inducing, promoting or otherwise modifying chemically induced or idiopathic cancers. The World Health Organization reported, in 2008, 12.7 million new cases and 7.6 million deaths, and a total of 107 agents, mixtures and exposure situations as carcinogenic to humans.[79] They noted that environmental causes of cancer include factors in the environment such as air pollution, ultraviolet (UV) radiation and indoor radon exposure but that "...every tenth lung cancer is closely related to risks in the workplace". These include complications due to environmental contaminants such as microcrystalline silica. Microcrystalline silica of respirable size is an acknowledged carcinogen, and exposure to quartz dusts in industry is a cause of chronic respiratory distress and increased incidence of lung cancer.[9,10] Radon is a colourless, odourless and tasteless natural radioactive gas released as a degeneration product of uranium that occurs naturally in all rocks, soils and deep in the Earth's core. Radioactive emissions are experienced at very low levels in homes and dispersed in the general environment but higher concentrations are experienced in metal mining, smelting and refining; the emissions are harmful and are recognised environmental factors impacting upon the incidence of environmental carcinogenesis.[80–84] The US EPA estimated that as many as 20,000 lung cancer deaths are caused each year by radon exposure and, in financial terms, an annual cost of more than $2 billion in direct and indirect health care costs. The values for action levels for environmental radon show a wide range, but concentrations between 100 and 400 Bq m^{-3} are used.[82] Radon exposure is now known to be largely responsible for lung tumours reported in miners of gold, tin and haematite.[9,83]

1.6 Lifestyle Factors

The so-called "lifestyle" factors, which are specific to certain races, geographical areas and socio-economic groups, present considerable difficulty in the evaluation of environmental and industrial carcinogens. The principal lifestyle factors encountered repeatedly in this review include:

- Cigarette smoking
- Alcohol consumption
- Locality of exposure (urban *vs.* rural communities, geographical areas, geophysical disasters)
- Demographic factors (age, sex, race, geographical area, *etc.*)
- Diet.[84,85]

Cigarette smoking amongst workers is a major lifestyle factor influencing the incidence of occupationally related lung cancers.[86–88] Cigarette smoking and exposure to mainstream smoke, passive inhalation of cigarette smoke in bars, casinos and other public places and exposure to cigarette-related products as a cause of lung cancer is a massive topic in itself, and outside the scope of the present review. However, it is important to recognise that:

- Most brands of cigarette contain significant residues of toxic metals, including cadmium, beryllium, mercury, arsenic and lead, together with at least 40 non-metallic mutagens, including benzene, benz[a]anthracene, napthalenes, dibenzo[c,g]carbazole, tobacco-specific nitrosamines and benzo[α]pyrene, all of which have been identified and classified as carcinogens through experimental studies in rodents[89,90]
- Wide variations exist in cigarette tobacco according to the areas in which it is grown and materials used in curing, processing, production and packaging[91,92]
- Local regulations relating to quality, refinement and production vary according to cigarette type
- The radionuclides polonium (^{210}Po) and uranium (^{235}U and ^{238}U) may occur in tobacco smoke.

All radioactive isotopes, as emitters of ionising radiation, are potentially carcinogenic, but levels present in most cigarettes are probably insufficient to have an impact upon the incidence of smoking-related lung cancers. Professor Stephen Hecht, an international expert in smoking-related cancer, drew up a list of harmful and potentially carcinogenic constituents of tobacco smoke or smokeless tobacco, filters and additives using criteria accepted by the IARC, EPA and NTP in the USA. He discussed, in detail, putative carcinogenic mechanisms for 20 hydrocarbons.[86,89]

1.7 Laboratory Models and Diagnosis

Animal models have been used in diagnostic and investigative medicine since the time of the ancient Greeks, and such notable names as Hippocrates, Galen of Pergammon and William Harvey used monkeys and dogs to study the circulation of the blood and the vascular network of arteries and veins.[93] With greatly improved refinement, animal models still have an important contribution these days in investigative medicine and there is abundant evidence that regulatory style animal studies provide a useful guide to the pathogenicity and carcinogenicity of metals/metalloids and related compounds.[10,44,66,94–97] They cannot provide a reliable surrogate for humans in predicting human risk from environmental carcinogens but there is good evidence illustrated throughout this volume to show that animal tests are complementary to human epidemiological studies and provide a useful guide to the pathogenicity where human studies do not exist or where observations are equivocal. Extrapolation of experimental results from animals will always be complex, subjective and equivocal and no non-human

species can realistically reproduce the wide racial, cultural, geographical, behavioural and genetic variability seen in the human race.

A large battery of tests in bacteria and in human and mammalian cell lines in culture have been developed over the last 50 years. They are designated for evaluation of the capacity of metals and metalloid ions and vast numbers of xenobiotic materials to evoke mutagenicity, DNA damage and other sub-cellular changes predisposing to malignancy.[43,98,99] In the absence of epidemiological or experimental animal studies, these *in vitro* genetic toxicology tests are helpful to regulators in making decisions as to which substances should be regarded as potentially carcinogenic to humans. They provide a data-base for use in structure–activity analyses.[98–100] The Ames *Salmonella* reverse mutation test was the first genotoxicity test recommended and experience shows that it will produce positive results for about 60% of genotoxic carcinogens (sensitivity $\sim$60%).[43,101,102] The late Professor Leon Golberg stressed to the American Medical Association, in 1979, that the Ames test for mutagens is able to tell us "little about the effects of chemicals in man and should be regarded only as a Litmus test; it ignores the fact that many suspected carcinogens are actually pro-carcinogens that require a specific triggering mechanism".[103] This triggering mechanism can be expected to produce derivatives capable of DNA interaction, mutagenic change, chromosomal damage, *etc.* as an integral stage in the multi-step process leading chemical carcinogenesis.[104,105]

The present volume aims to present a critical re-evaluation of clinical and experimental data upon which judgements on the carcinogenic properties of metals and metalloid elements are made. The toxicity of elements emitting ionising radiation is a large and specialised subject and not within the scope of the present book, but all radioactive isotopes are known human carcinogens as documented in IARC *Monographs*.[106] To illustrate certain clinical problems, reference is made as appropriate to certain radio-isotopes, including thorium, gold (^{195}Au and ^{198}Au) and other metals used in diagnostic and experimental medicine. As improved investigation, and wider chemical and toxicological knowledge comes to hand, so improved environmental and industrial regulation achieves improved human health and safety.

In the past 20 years, specific health problems with implications of carcinogenicity have led to considerable research and controversy. For completeness, the present discussion addresses the basis and possible resolution of public concerns relating to risk associated with such problems as:

- Metal-on-metal prostheses and metal implants
- Aluminium-related breast cancer
- Semiconductor exposure
- Silicone breast implants
- Antimony oxide as a flame retardant in cot mattresses
- Nanotechnology and its impact on human health.

The EPA and National Institutes of Health in the USA and the Scientific Committee on Emerging & Newly Identified Health Risks (SCENIHR) in

Europe meet regularly to discuss current issues and publications are available for consultation on these and other issues of public interest and concern. The report of the SCENIHR in March 2007 relating to preliminary opinion on "*The appropriateness of the risk assessment methodology in accordance with the Technical Guidance Documents for new and existing substances for assessing the risks of nanomaterials*" is one example.[107]

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Part 1
Elements of Importance as Nutrients

CHAPTER 2

Iron

2.1 Introduction

Iron has been known to man for longer than most other elements. Artefacts have been recovered from human civilisations of the "Iron Age" 3000 years ago, but evidence of early mining dates from prehistoric times. Iron is a transitional metal and the fourth most abundant element in the Earth's crust. It exhibits two main oxidataion states, Fe(II) and Fe(III), and compounds of both are found naturally. Iron is also relatively abundant in the universe and asteroids and much of the Earth's core is composed of iron. Large quantities of iron have been recovered from meteoritc debris. Iron deposits are commonly seen as black sands along beaches and stream banks.

Iron is mined mainly as haematite (Fe_2O_3) in Europe, North and South America and China (Figure 2.1), but other ores including magnetite ($Fe_2O_3 + Fe_3O_4$), iron pyrites (FeS_2), goethite, limonite or siderite, and taconite (a low-grade siliceous iron) are more prevalent naturally in certain areas. Banded iron formations (BIF) of taconite found in North America are fine-grained metamorphosed sedimentary rocks composed predominantly of magnetite and silica (as quartz). Iron ore deposits are frequently associated with vanadium, aluminium and titanium but health concerns amongst miners have increasingly been associated with exposure to radon and radon daughters, silaceous dusts and arsenic poisoning. Lead poisoning is an additional hazard. Nowadays, iron and ferrous metals (cast iron, carbon steel, high speed steel, *etc*.) have a vast range of industrial uses in engineering, automotive manufacture, structural components in building, and steels with specific properties of hardness, durability, tensile strength, resistance to corrosion and malleability.

Many thousands of workers are exposed to iron in industrial dusts, aggregates and fumes in mining pits, ore crushing and grinding, extraction processes, furnace working, smelting, refining, steel works and other iron-related industries. Siderosis, pneumoconiosis, silicotuberculosis and other respiratory

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Figure 2.1 Haematite (from the West Cumberland Minefield).

diseases are prevalent in workers employed in haematite mines where blasting and pneumatic drilling are commonly used to release iron ore from hard rock (see Figure 2.2, below).[1–3] Pulmonary and tracheal cancer is an industrial hazard in iron (haematite) mining but levels of risk vary greatly according to geographical area, the type and duration of working in the pits, safety procedures in operation (including effective dust control systems, face masks and high-pressure mist systems), and the nature of environmental contaminants such as radon, carbon monoxide and methane gas.[4,5] Considerable efforts have been made in recent years to control cancer risks in iron mining and related industries, and local and national authorities publish stringent guidelines. Ferrous metals are magnetic and contain variable amounts of carbon and other metals including nickel, chromium, cadmium, vanadium and tungsten to improve tensile strength, resilience, resistance to corrosion and other physical properties. Many of these metal additives are toxic and potentially carcinogenic in humans and other animals. Stainless steel, for example, comprises 18% chromium and 8% nickel to provide a characteristic resistance to corrosion. The most commonly used ferrous metals include cast iron, mild steel, high speed steel, stainless steel and high tensile steel.

Iron is an essential nutrient for most living organisms, with key roles in cell physiology, proliferation and functional differentiation, haemoglobin synthesis and blood quality, oxygen transport, resistance to stress and disease, immunomodulation, synthesis of myoglobin and oxygen supply to muscles, and prevention of fatigue.[6–8] The human body contains 3.5–4 g of iron, most being bound in haemoglobin in circulating erythrocytes, but some is stored in the liver, muscle and reticuloendothelial tissues. The human body has no

means of excreting iron, and regulation is principally through limiting intestinal absorption or through iron loss in perspiration, desquamation of epidermal keratinocytes, nail and hair growth. Human requirements for iron are provided by dietary intake (red meat, vegetables, cereal, nuts, seafood, *etc.*), although in clinical cases of iron deficiency anaemia parenteral injection of iron supplements including iron dextran, iron sucrose and preparations of ferrous sulfate, ferrous fumarate, ferrous gluconate and polysaccharide–iron complexes is available. These are beneficial for those patients unable to tolerate oral iron supplements, but, as discussed below, controversy exists over their capacity to invoke injection site tumours and other complications.[9–11]

A third and worrying aspect of iron toxicity concerns the iron-overload conditions such as the hereditary and idiopathic haemochromatoses, which have been associated with hepatocellular carcinoma and possibly breast cancers.[12,13] Dietary iron overload was first described by Strachan in 1929 in peoples of sub-Saharan Africa. It seems that these people were accustomed to drinking home-brewed beer with a high iron content.

Iron interacts with other metals in the body, largely as a result of ion binding in the intestinal mucosa, circulation and elsewhere. Ferritin is a major iron-binding protein that will bind aluminium, zinc, beryllium, cadmium and copper in a competitive fashion.[14–16] Iron interacts with cobalt and nickel in intestinal uptake, which is modulated by vitamin C.[17,18] The role of iron in haem synthesis is impaired by the action of lead and possibly nickel in inhibiting the essential enzyme delta-aminolaevulinate dehydratase in bone marrow, and thus erythroid cell differentiation.[19–22] This is a reliable and quantitative indicator of lead exposure in humans.

2.2 Iron in Human Nutrition

McCance and Widdowson first demonstrated the essentiality of body iron-balance and metabolisable iron for normal health and tissue oxygenation through regulation of haemoglobin synthesis erythropoietin and serum proteins.[23] Iron plays a fundamental role in the growth and functional maturation of all tissues in the human body, principally through its role in haem synthesis and oxygen-carrying function in the blood, but also in DNA synthesis, immune responsiveness and enzymes regulating energy metabolism.[6–8,24–27] Iron (Fe) plays a critical role in cell proliferation, and Fe deficiency results in G_1/S-phase arrest of the cell cycle and apoptosis. However, the precise role of Fe in cell-cycle control remains unclear.[27]

Iron is absorbed intestinally by ferrous ion Fe(II)-binding cell surface receptors, endocytic vacuolation and intracellular ferritin binding. Ferric iron Fe(III) is reduced to ferrous ion in the acidic medium of the stomach and in the presence of ferri-reductase. Iron absorption is intimately linked to a specific transporter protein, Nramp-2/DCT1, which is upregulated in states of iron insufficiency and chronic hypoxia.[28] A further basolateral intestinal membrane transporter, ferro-oxidase (hephaestin), has been identified. This is a

caeruloplasmin-like protein involved in the efflux of iron from intestinal epithelial cells. Subsequent metabolism of Fe(II) involves a sequence of intracellular co-ordination complexes involving low molecular weight transferrin-carrier proteins and incorporation into mitochondrial and intracellular enzymes. One or more of these co-ordination complexes may involve linkage to water molecules or molecular oxygen as required in the oxygen-transporting function of haemoglobin. Intestinal iron absorption modulated through the action of vitamin C and iron-binding proteins, such as transferrin and lactoferrin, is probably regulated by body demands for iron or through hormonal action.[8,17] In humans, most of the body iron is bound within erythrocytes, with lower concentrations in bone and soft tissues. Homeostatic mechanisms controlling iron metabolism in the human body are unclear. Intestinal iron absorption is impaired by chelators including phytate, phenolic compounds and plant fibres in the diet, or through competitive inhibition by lead, cadmium, nickel and cobalt binding at intestinal receptor proteins.[26,29] Ethylenediamine tetraacetic acid (EDTA) has good iron-binding capacity. Iron-containing dietary supplements and parenteral iron are readily available to treat iron deficiency anaemia and related conditions.[30] As discussed in more detail later, iron supplements such as iron–dextran are a cause of concern on account of their ability to evoke anaphylactic reactions, and injection site sarcomas in rats.[31]

Much is still unclear regarding the function of carrier proteins in iron homeostasis, but recent research suggests that extracellular transferrin functions as a primary iron carrier protein, regulating its availability and mobilisation in ferro-enzyme synthesis, energy metabolism, synthesis and transcription of RNA and DNA, and production of nucleotides, hormones and neurotransmitters.[6] Ferritin modulates intracellular iron storage and serves in binding and protecting tissues from excess iron. Ferritin synthesis is stimulated through increased demand for iron in inflammatory conditions, stress, mitosis, cell differentiation and repair processes.[9,32] Increased ferritin levels have been reported in some cancer cells without corresponding increases in iron-binding capacity. Recent research suggests that abnormalities in molecular upregulation of ferritin synthesis in cancer cells can deregulate iron homeostasis.[33,34]

In vitro studies in hybridoma cells show that increased cell membrane permeability to Fe(II) raises lipid peroxidise synthesis and iron storage, and leads to oxidative stress and DNA base modifications.[35] In non-neoplastic cells, intracellular iron is critical in controlling the mitotic cycle, notably completion of the S-phase of DNA replication, respiration and oxidative phosphorylation through the action of mitochondrial ferro-enzymes and electron-transport proteins.[9] Intra- and extracellular iron balance activates transferrin in the differentiation and maturation of lympho-myeloid cells in culture. In children with iron deficiency anaemia, consistently low apoptotic responses in neutrophils and monocytes are normalised by iron therapy.[36] Inhibition of iron transport and iron deficiency syndrome resulting from desferrioxamine binding or other chelators leads to decreased mitosis in erythropoietic tissues.[37]

Lead (Pb)(II) is a well known ferro-enzyme inhibitor, and depletion of δ-aminolaevulinic acid, dehydratatase ferrocheletase and other enzyme-dependent events results in disturbed iron homeostasis and anaemia.[19–22] Depletion of ferro-enzymes serves as a biomarker for lead exposure.

High iron intake can cause intestinal damage and impair copper and zinc uptake but importantly the association between chronic high iron levels in diet and colorectal cancer is a cause for concern. Whilst the full extent of the problem is unresolved, it is predicted that long-term induction of reactive oxygen species via the Fenton reaction may lead to cell damage as a consequence of lipid peroxidation and oxidative DNA and protein damage, and ultimately genomic instability and cancer.[38,39]

2.3 Occupational Exposures and Carcinogenic Risk in Haematite Mining

Although products made of iron and ferrous metals are encountered in everyday life, the greatest toxic risks of cancer are encountered in the mining and iron extraction, smelting and foundry industries (Figure 2.2). Workers are exposed to haematite dust in deep mines where blasting and pneumatic drills have been in regular use since the 1920s. The risks of cancer through iron exposures in surface workers and those employed in building and construction industries, automobile and aircraft manufacture, tool and equipment production and pigments for use in paints, plastics, printing, ceramics and textiles are similar to national averages. However, epidemiological and statistical evidence from studies in Europe, Asia and North and South America show conclusively that occupational exposure to haematite dust and mine contaminants increases the risk of lung cancer.[1,2,5] The cancer risk is significantly higher amongst underground workers but not surface workers, and over the past 50 years at least, there has been considerable debate over the principle causative factor(s). The discussion focuses upon whether increased lung cancer is attributable to inhalation of:

- Ferric oxide (haematite) dust
- Carcinogenic metal/metalloid contaminants
- Silica dust
- Radon and radioactive emissions
- Cigarette smoking
- Or to a combination of more than one cause.

An early statistical evaluation of risks encountered in haematite mining in four Cumberland pits in the UK over the period 1948–1967 showed that, of 5811 miners over the age of 15 dying in the 20-year period, 42 deaths were attributable to lung cancer, 74 to other cancers and 174 to respiratory diseases.[40] Risks of lung cancer varied widely according to profession but the number of lung cancer deaths observed was 50% higher than expected among all iron miners (underground and surface workers); cancers in other tissues and presumably

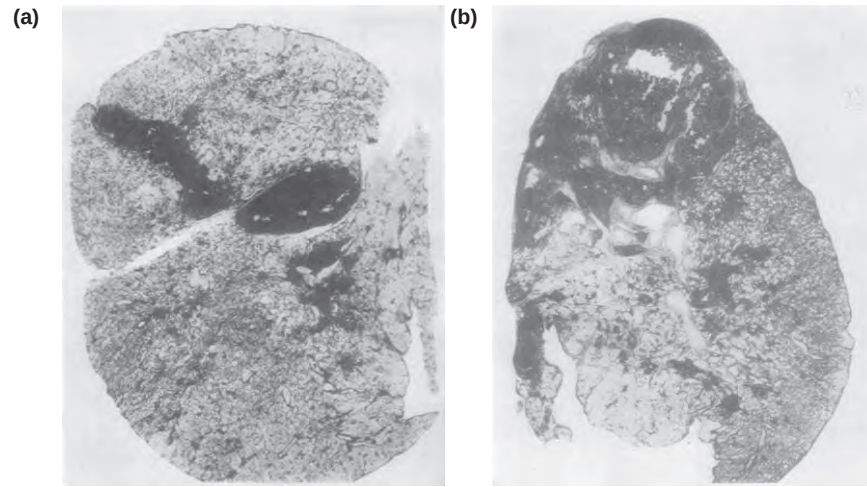

Figure 2.2 Pneumoconiosis or siderosis: lung pathology in Durham iron miners. The pictures show a histological profile of iron particles conglomerated in the lung alveoli at low and high power magnification: (a) progressive massive fibrosis involving the upper lobe and upper part of the lower lobe (P.M. 5016); (b) advanced stage of progressive massive fibrosis (P.M. 2939). (Reproduced from Faulds, *J. Clin Path*, 1957, **10**, 187.)

Table 2.1 Comparison of observed and expected mortality among iron mine employees in Cumberland mines 1947–1967. (Numbers expected from national experience in parentheses.)

	Clinical observation		
Profession	*Lung cancer*	*Other cancers*	*Respiratory disease*
Underground workers	36 (21)	65 (59)	159 (60)
Surface workers	6 (7)	9 (17)	13 (16)
All iron miners	42 (29)	74 (75)	174 (76)

attributable to other causes were similar to national averages (Table 2.1). The statistics also showed that miners working underground were exposed to a 75% higher risk of lung cancer mortality. Post-mortem reports of lung cancer fatalities in the Cumberland pits showed that most of the cancers seen were of the ''oat-cell'' type, a tumour type prevalent in uranium miners exposed to radioactive emissions.[41] Coal mining in Cumberland and elsewhere involves exposure to silica dust, haematite dust and radon.[42] There is no doubt that cigarette smoking amongst miners was a contributory factor in lung cancer incidence, but this was not shown on the *post-mortem* reports analysed.

Inhalation of haematite iron oxide *per se* is not considered by Boyd *et al*. to be a major cause of lung cancer in miners,[40,43] although it does pose a serious risk of pneumoconiosis and pulmonary fibrosis, with silica dust.[1] Siderosis caused by the retention of haematite dust in pulmonary and tracheal epithelia