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HUMAN HEALTH EFFECTS OF ENVIRONMENTAL POLLUTION (KC MAKRIS, SECTION EDITOR)

Metalliferous Mine Dust: Human Health Impacts and the Potential Determinants of Disease in Mining Communities

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Abstract

Purpose of Review Many factors influence the health impact of exposure to metalliferous mine dusts and whilst the underpinning toxicology is pivotal, it is not the only driver of health outcomes following exposure. The purpose of this review is twofold: (i) to highlight recent advances in our understanding of the hazard posed by metalliferous mine dust and (ii) to broaden an often narrowly framed health risk perspective to consider the wider aetiology of the potential determinants of disease.

Recent Findings The hazard posed by metalliferous dusts depends not only on their abundance and particle size but other properties such as chemical composition, solubility, shape, and surface area, which all play a role in the associated health effects. A better understanding of the mechanisms that lead to toxicity, such as recent advances in our understanding of the role played by reactive oxygen species (ROS), can help in the development of improved in vitro models to support risk assessments, whilst biomonitoring studies have the potential to guide risk management decisions for mining communities.

Summary Environmental exposures are complex; complex geochemically and complex geographically. Research linking the environment to human health is starting to mature, highlighting the subtlety of multiple exposures, mixtures of substances, and the cumulative legacy effects of life in disrupted and stressed environments. We are evolving more refined biomarkers to identify these responses, which enhances our appreciation of the burden of effects on society and also directs us to more sophisticated risk assessment approaches to adequately address evolving regulatory and societal needs.

Keywords Exposome · Bioaccessibility · Biomonitoring · Mining legacy · Risk assessment

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Introduction

'We have been mortgaging the health of future generations to realise economic and development gains in the present' [103].

Environmental pollution contributed to an estimated 9 million deaths and significant economic losses across the world in 2015 [62]. Indeed, *The Lancet* Commission on pollution and health identifies pollution as the largest environmental cause of disease and premature death [62]. Metalliferous mine dusts, and associated potentially toxic elements (PTEs) released into the environment through dust generating mining activities, is one such environmental pollution related cause of adverse health effects to humans. Despite occupational improvements within the mining industry, the release of metalliferous dusts into the environment remains a human health issue, especially in regions with poorly developed regulatory systems and where historic mining has left a significant legacy of exposed metalliferous mine wastes. The recovery of economically valuable metals present in historical waste materials also presents new technological and environmental challenges, whilst informal practices, such as those adopted in the artisanal mining of gold, also result in high levels of exposure to metals [14].

We review recent studies on the nature and hazard characterisation of metalliferous mine dusts (e.g. their main sources, composition and characterisation). Many factors influence the health effects of metalliferous mining dusts and understanding the exposure pathways is critical, as is the source, transport pathway, nature of the exposure (e.g. duration, activity) and exposure route (i.e. by inhalation, ingestion or dermal/topical absorption). The amount of any substance taken into the body that ends up active within the body is also an important consideration in the assessment of risk. The dose taken in by inhalation, ingestion and touch may not be the same as that retained within the body as varying amounts can be excreted quickly by different routes, usually through the liver, kidney or gastrointestinal tract, but sometimes in sweat, skin cells and hair loss [13].

Whilst the underpinning toxicology is pivotal, it is not the only driver of health outcomes following exposure, and we broaden an often narrowly framed health perspective to consider other potential determinants of disease, such as the role played by genes, lifestyle choices, and the wider socio-economic context. Where we make reference to the underlying toxicological data and biological processes that underpin many of the related health disorders, we do not do so in detail. Readers are referred to the key public health and medical literature on which this review has drawn.

Consideration needs to be given to the fact that each location, and each population, are different, as are the variety of exposure scenarios (e.g. occupational exposure, neighbourhood exposure, population exposure), further complicated by differences in the management of the hazards. The complex nature of, and exposure to, metalliferous mine dusts requires approaches that take this complexity into account if we are to correctly apportion and mitigate the impacts on human health. There is a key role here for those working at the public-environmental health nexus to (i) develop a better understanding of the common predicators of ill health, (ii) to identify how to recognise which differences (be they individual, social, cultural, environmental) need special attention, and (iii) harness advances in laboratory sciences and technology to better utilise big data to support these needs. We highlight the challenges, as well as the opportunity, for new integrated environmental health tools to support future management.

Source and Environmental Pathways of Metalliferous Mine Dusts

PTEs frequently associated with mined deposits, or as gangue minerals in ore deposits, include arsenic (As), cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), lead (Pb), mercury (Hg), nickel (Ni), uranium (U), and zinc (Zn), (Table 1). Whilst several of these PTEs (such as Cu and Zn) are essential for life, this paper only considers toxic or excess exposures. Due to their high toxicity, As, Cd, Hg, and Pb rank among the top 10 priority substances that are of public health concern ([12]–2018). Other priority elements for human health concern, and of particular relevance when considering exposure to metalliferous mine dust, include U and the transition metals Co, Cu, Ni and Zn due to their ability to generate reactive oxygen species (ROS) in biological tissues via Fenton-type reactions [25, 48, 63]. The Fenton reaction refers to the reaction between hydrogen peroxide and ferrous salts to produce a reactive species capable of oxidising a wide variety of organic substrates. In addition, we also include iron (Fe) as Fe-bearing minerals are commonly found in mining dust and Fe oxides found in dust are potential contributors to inflammation in the human lung [43]. The common crystalline and amorphous phases of these PTEs found in ores or/and mine-related wastes are listed in Table 1. Mining activities provide multiple pathways for both the generation and distribution of mineral dusts into the environment. Dusts are released from a range of mining-related activities such as removal of the overburden, extraction and refining operations (e.g. smelter emissions; slag piles and tailings), and other ore-handling operations [23], all creating large volumes of dust that are readily mobilised by aeolian (wind-related) processes and can result in atmospheric transport over large distances [59]. Dust generation also occurs when transporting wastes, both on haulage roads within, and around, the mines, but also over longer distances such as along train lines [61]. Widespread contamination associated with airborne emissions from active and legacy mining and smelting operations is well documented in the literature, reported across a wide range of sampled media, including attic dust [16, 21]; house dust [75]; atmospheric dust [49•]; road dust [97•]; crop/vegetables [101]; surface and groundwater [94], with mining-

Table 1 Potentially toxic elements (PTEs) in metalliferous mine dust and the common crystalline and amorphous bearing phases

PTE	Common bearing phases
As	Arsenopyrite (FeAsS) is the main As ore mineral and is often found in gold ores; scorodite and iron arsenate (Fe_3AsO_7) are secondary phases in tailings[1]; calcium arsenate on fly ash was found to be associated to the combustion of pyrite enriched coal; arsenic trioxide in particulate form was found in close proximity to smelters and roasters.[2]
Cd	The primary ore of cadmim is the zinc mineral sphalerite; other important Cd-bearing minerals are greenockite (CdS) and hawleyite (CdS); Fe oxides such as pyrite usually contain important amounts of Cd.[3]
Co	Cobalt is almost always a by- or co-product of mining for other base metals, chiefly nickel and copper; cobaltiferous iron sulphides include pyrite (FeS_2) and pyrrhotite ($Fe,Co)_{1-x}S$; other Co-bearing sulphides are cobaltite (CoAsS), erythrite ($Co_3(AsO_4)_2{\cdot}8H_2O$), carrollite $Cu(Co,Ni)_2S_4$, linnaeite Co_3S_4, pentlandite $(Fe,Ni,Co)_9S_8$ and siegenite $(Co, Ni)_3S_4$.[4]
Cr	Chromite is by far the most industrially important mineral for the production of metallic chromium; magnesiochromite (MgCr2O4) is a minor ore mineral.[5]
Cu	Chalcopyrite ($CuFeS_2$), chalcocite (Cu_2S), and bornite (Cu_5FeS_4) are important ores; siderite ($FeCO_3$), cuprite (Cu_2O), malachite [$Cu_2(CO_3)(OH)_2$], azurite ($Cu_3(CO_3)_2(OH)_2$), are minor copper ores.[6]
Fe	Pyrite (FeS_2), haematite (Fe_2O_3), magnetite (Fe_3O_4), goethite [α-FeO(OH)], and limonite ($FeO(OH){\cdot}n(H_2O)$ are important ores; pyrite Fe oxides and Fe-Mn oxyhydroxides are common hosts of PTEs such as As, Cu and Ni.[2,7]
Hg	Cinnabar (HgS) is the main ore mineral; others include elemental mercury, corderoite ($Hg_3S_2Cl_2$), schwartzite [$(HgCuFe)_{12}Sb_4S_{13}$], and livingstonite ($HgSb_4S_7$)[8]; coal mining wastes have high Hg contents[9]; loss of elemental Hg occurs during amalgamation processing of ore from lode and placer Au deposits.[10]
Ni	Pentlandite [$(Fe,Ni)_9S_8$.] is the most important nickel sulphide mineral and is often associated with nickel-containing pyrrhotite and chalcopyrite. Other nickel-bearing minerals include nickeliferous limonite, nickeliferous goethite, siegenite, and millerite; Ni-Fe alloys, glass and olivine were found in waste dusts (slags, fly ash) generated by laterite Ni ore smelting.[11]
Pb	Galena (PbS) is the main lead ore mineral; anglesite ($PbSO_4$), cerussite ($PbCO_3$), coronadite ($Pb_2Mn_8O_{16}$) and pyromorphite ($Pb_5(PO_4)_3Cl$) are common secondary phases.[12,13]
U	Uraninite (UO_2) is the most important ore of uranium; other U-bearing minerals include autunite [$Ca(UO_2)_2(PO_4)_2{\cdot}10–12H_2O$], coffinite [$U(SiO_4)_{1-x}(OH)_{4x}$], carnotite ($K_2O{\cdot}2UO_3{\cdot}V_2O_5{\cdot}nH_2O$), tyuyamunite ($CaO{\cdot}2UO_3{\cdot}V_2O_5{\cdot}nH_2O$), schoepite [$(UO_2)_8O_2(OH)_{12}{\cdot}12H_2O$], torbernite [$Cu(UO_2)_2(PO_4)_2{\cdot}8–12H_2O$], and uranophane [$Ca(UO_2)_2(HSiO_4)_2{\cdot}5H_2O$].[14]
Zn	Sphalerite (ZnS) is the main zinc ore mineral; sphalerite (ZnS) is the main zinc ore mineral; other Zn-bearing minerals include hemimorphite [$Zn_4Si_2O_7(OH)_2.H_2O$], smithsonite ($ZnCO_3$), hydrozincite ($Zn_5(CO_3)_2(OH)_6$).[15]

[1] [4]; [2] [72]; [3] [110]; [4] [50]; [5] [18]; [6] [80]; [7] [74•]; [8] [87]; [9] [6]; [10] [7]; [11] [38]; [12] [111]; [13] [9]; [14] Hettiarachchi et al. 2018; [15] [109]

related particulates reported in soils adjacent to mines and across the towns of mining communities [44,]. The unregulated informal recycling of the complex contaminant mixtures arising from Waste Electrical and Electronic Equipment (WEEE) also releases metalliferous dusts associated with precious metals and rare earth elements, mixed with organics and plastics found in such equipment [24•].

Wherever mining has taken place then there is a potential legacy of exposed wastes, the literature attests to multiple ongoing health risks for people and the wider environment associated with many abandoned mine sites and un-remediated tailings. Many legacy sites contain relatively high concentrations of metals and metalloids, often up to several percent by mass, and the economic value of these metals and their role as part of a circular economy, are becoming increasingly recognised [30]. Where former mine sites and waste deposits are the focus for the recovery of economically valuable metals, then the industrial activity can be a more complex

issue (i.e. re-working spoil heaps/lagoons/leachates) []. In addition, the materials have been weathered and subjected to a wide range of environmental conditions that have modified the original ore and gangue materials. In such contexts, the dusts generated are potentially different in their reactivity and hazard from the originally mined sources. Parallels can be drawn with the coal mining industry where changes in specific dust characteristics have been invoked to explain resurgence in diseases such as black lung in the Appalachians [10].

PTEs can be transferred from mine dust-impacted soil to the human body via unintentional ingestion of soil and the soil-plant-human food chain. Children are at particular risk of ingestion of contaminated soil due to their frequent hand-to-mouth activity. Children are also sensitive receptors since girls are born with all their eggs already in their ovaries: contamination of young girls affects their children and probably their grandchildren. Evidence also suggests that although sperm is generated daily after puberty, there is also transmission to the next generation of some early life exposures through epigenetic mechanisms, although the evidence is currently limited to obesity, stress, risk of diabetic death, cardiovascular diseases and the like [40••]. It is possible that environmental metals may be added to known epigenetic toxins such as endocrine disruptors, but further work is awaited [71]. Furthermore, there is a difference between intergenerational (or parental) and transgenerational effects. The former include effects such as the impact of in utero exposure to toxins on the developing embryo and its germline, whilst the latter refers to effects found in generations not exposed to the initial exposure, e.g. great-grandchildren [40••, 83•].

The relationship between outdoor mining-related metal contamination and the indoor residential environment remains poorly understood. Quantifying indoor concentrations of metals originating from mine waste is complex; however, house dust is an important route of exposure, particularly for children. Numerous studies highlight the increased risks for long-term residents of communities living close to active, re-activated and abandoned mine sites around the world (e.g. [115•]).

Characterisation of the Complex Nature (Hazard) of Metalliferous Dusts

Hazard, in this context, refers to the inherent properties of the mineral dust that have the potential to cause harm. Epidemiological and toxicological studies have indicated that the hazard posed by mineral dusts depends not only on their abundance and particle size but other properties such as their chemical composition, solubility, shape, structure and surface area of the inhaled particles, which all play a role in the associated toxic, carcinogenic or other health effects [88•, 89•]. Furthermore, whilst we hypothesise that organs such as the lungs where already damaged by disease processes will be more susceptible to the absorption of metals and other toxins, to the authors' knowledge little is known about how existing disease affects the outcome of exposure to metalliferous dusts.

In relation to dusts, size matters. Whilst most mining operations generate coarse dust (≥ 2.5 μm diameter), high-temperature processes, such as smelting and coal combustion, are typically associated with the generation of fine particulates (≤ 2.5 μm) [31]. This fine fraction can travel long distances and an understanding of respiratory tract anatomy, physiology and clearance mechanisms are also important to understand the exposure and dose. The respiratory tract in humans is typically split into three regions (after [27••]): (1) the extrathoracic region, which includes the nasopharynx and airways to the larynx. There is also the potential for the direct transfer of particulate matter (PM) through the olfactory (smell) nerves from nose to brain (2) the tracheobronchial region, which consist of the large upper airways from the larynx down to before the terminal bronchiole, with the upward mucociliary transports, and (3) the pulmonary region, defined as the terminal bronchioles and the alveoli. Following inhalation, the larger inhaled particles become trapped in the mucus that lines the airways and are transported (by tracheobronchial cilia) and expectorated or swallowed into the gastrointestinal pathway. Particles < 4 μm are respirable (i.e. deposit in the alveoli). The lungs act as a continuous sampler of inhaled PM. Humans are oronasal breathers, and there is less filtering of PM inhaled through oral breathing compared to nasal breathing. With greater exertion, more oral breathing results, and thus ventilation rates and activity patterns need also to be considered in different modelling exposure scenarios.

Whilst a growing body of literature underlines the increasing concern for the impact of dust PM, especially the $< PM_{2.5}$, $_1$ and $_{0.1}$ fraction, on human health, to understand the nature of the hazard posed the mineral dust should be suitably characterised. Growing acceptance that the physicochemical nature of the PM influences the deposition, dissolution and distribution to other parts of the body, and ultimately the toxic effect, has seen an expansion in approaches to PM characterisation to explore the chemistry, oxidation states and material structure [48]. Synchrotron-based X-ray fluorescence and X-ray absorption spectroscopy (XAS) are increasingly being used to map the mineralogy, phase composition, elemental associations, and oxidation states of a range of elements contained within the PM, whilst the use of sequential chemical extractions remains a popular tool for solid-phase speciation (e.g. [93, 110]).

The need to utilise multiple techniques to reveal the complex nature of these dusts, and the complex nature of the interaction with health, is now widely recognised. The exposome is one such approach [32•]: the total exposure of a person from conception to death and the resulting health impact. Although complex, with needs for identified biomarkers,

new statistical and analytical approaches, and often based on large datasets, the exposome can also work with smaller samples (435 adolescents, 19 metals: [85•]). Our classification of determinants of disease is similar to the current classification of the exposome: internal, specific external, general external [32•], but focussed on metalliferous dusts and mining (Fig. 1).

A growing body of work highlights examples of in vivo reactions that can generate an overabundance of reactive oxygen species (ROS), reactive nitrogen species (RNS) and lipid peroxidation in the body. Reactive molecules are pivotal to control cellular responses focusing on inflammatory settings and associated with many pathological conditions such as chronic inflammation, atherosclerosis, diabetes, inflammatory bowel disease and autoimmune diseases [86]. ROS are necessary intracellular signalling molecules which regulate a wide variety of physiology; however, an overabundance of ROS can lead to oxidative stress within the body. Fe-rich particles may also contribute to increased ROS formation. Iron exhibits Fe^{3+} and/or Fe^{2+} forms in crystalline oxides and inhalation into the human lung of Fe-containing particles has been associated with the release of free radicals [67•]. Magnetite has been reported to be a more effective catalyst for Fenton reactions and the production of OH radicals than goethite or haematite. The iron oxidation state of most natural iron oxide minerals such as goethite and haematite is 3+, whilst magnetite has a combination of Fe^{2+} and Fe^{3+} oxidation states; the reaction rate of H_2O_2 with Fe^{2+} sites is significantly higher than the rate with Fe^{3+} sites [92]. Oxidative stress can result in a range of negative outcomes, including DNA damage, chronic inflammation in the lungs [82] and cardiovascular disease [58••].

'Risk' is the possibility of *harm* arising from a particular exposure to a substance or substances, under specific

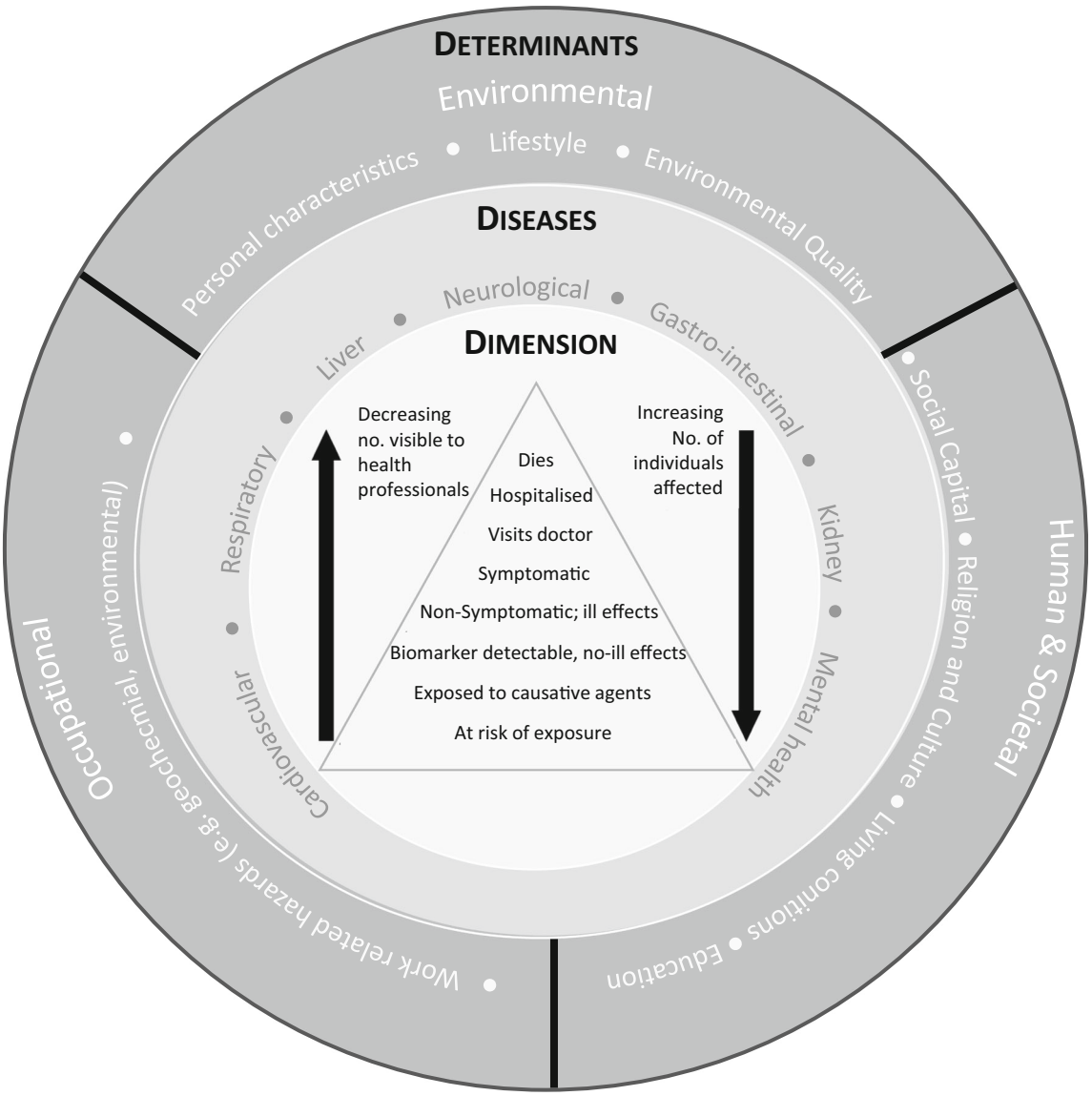

Fig. 1 Mining-related determinants of disease, associated diseases, and dimension (scale) of the disease burden (the 'disease pyramid'© is after [96••])

conditions. In assessing risk to humans following exposure to a contaminant, it is the quantitative pattern of the deposition, and subsequent bioavailability (uptake), that influences the dose, and ultimately the toxic effects, rather than the exposure concentration (intake) per se [27••]. For the inhalation pathway, we need to understand the behaviour of inhaled particles; not just the initial dose but how the PM is cleared and redistributed within the body. Significant research has focussed on the development of in vitro non-animal testing and biomonitoring methodologies to provide human-relevant data for decision support in risk assessments and notable recent approaches are outlined below.

Physiologically-Based In vitro Lung Bioaccessibility Protocols

In vitro bioaccessibility refers to that portion of the contaminant which can be extracted and released during passage through the human system being represented/modelled and is thus available for uptake. Several in vitro protocols have been developed, such as the BARGE UBM [106] and US EPA glycine method [99] for oral bioaccessibility modelling. Despite the often complex dissolution kinetics, in vitro oral bioaccessibility protocols may be used as an indicator of in vivo bioavailability, with mathematical equations relating in vitro bioaccessibility to in vivo bioavailability for a range of soil types, sources and PTEs. Similar in vitro–in vivo validation for inhalation bioaccessibility protocols are still lacking. Boisa et al. [22] highlight some of the many problems with using simulated lung fluids. Nonetheless, the last two decades have seen a proliferation of experiments using simulated lung fluids. This research has predominantly focussed on two main types of fluids: those representative of the neutral extracellular environment in the interstitium of the lungs (i.e. Gamble's Solution (GS) believed to mimic the interstitial conditions of the lungs; the interstitium is the space between cells, a matrix of collagen bundles interspersed with fluid), or the more acidic artificial lysosomal fluid (ALF) which simulates the environment within the spaces of the pulmonary alveolae where cells engulf and metabolise particles. This research, whilst predominantly on air pollution (which contains combustion-related metals and hence of relevance), highlights that particles deposited in the lungs that are not readily solubilised by the epithelial lining fluids (i.e. the fluids covering the lung lining) will be subject to phagocytosis by the pulmonary alveolar macrophages. Complexation with biological components in the lung fluids can also influence dissolution rates [22], and once dissolved can negatively impact the immune system [36, 100].

Different solubilities and dissolution rates in different body fluids [44, 57], interactions of complex chemical mixtures [26•], and the role of enzymes, mucoproteins and surfactants are increasingly being investigated [19, 65]. The role of mineralogy and soil-phase speciation in the bioaccessibility and bioavailability of metals in PM is well documented [38]. U-enriched aeolian dusts in the proximity of two U mines in New Mexico highlights the differential solubility of U minerals; uraninite and carnotite are more soluble in the GS compared to the more acidic ALF [49•]. Whilst such extraction protocols still need in vivo validation, the authors demonstrate the extracts accord with a geochemical model (PHREEQC). Acknowledging the potential continuation of metal(loid) dissolution once the PM is cleared from the lungs and/or has passed through the gastrointestinal tract has rarely been addressed. Kastury et al. [57] recently proposed an inhalation-ingestion bioaccessibility assay, designed to be biologically relevant to a human inhalation scenario.

In vitro Inhalation Toxicity Testing Using Cell Cultures

Non-animal models of epithelial barriers (skin, intestinal and pulmonary context) play a critical role for in vitro to in vivo extrapolation. Immortalised human adenocarcinoma cell lines (such as Caco-2 or T84) help to study absorption mechanisms, as do immortalised cell lines (e.g. BEAS-2B cells) and primary epithelial cells (e.g. normal human bronchial epithelial cells). However, as adenocarcinoma cell lines are derived from tumours, which by their nature are less representative of typical conditions, the intestinal epithelial cells may potentially offer a more physiologically relevant cell-based approach [42••].

The inflammatory stress response (ISR, used as a measure of particle toxicity) was investigated in human lung epithelial cells following exposure to a range of metal-sulphide ore minerals: the role of Fenton and other heavy metals was highlighted, whilst copper-bearing ore minerals, containing ferrous-iron, produced the largest ISR [48]. An earlier study highlighted the role of pyrite in coal workers' pneumoconiosis with pyrite-free coal producing the same limited ISR as exposure to inert organic matter [47].

The elevated presence of ROS can lead to oxidative damage of biomolecules, in turn, linked to a range of diseases including cancer, respiratory, neurodegenerative and digestive disorders ([58••, 66]). The body's stress response to ROS can also generate excess ROS in the lungs, engendering a vicious negative cycle. The oxidative potential of PM_{10} in urban air samples collected on filters across Lanzhou using plasmid scission assay (PSA), in tandem with total and water-soluble metal extraction, showed a negative relationship between TD_{20} (toxic dose of particles necessary to damage 20% of DNA) and all of the metals investigated, with the water-soluble Cu, Zn, As and Mn exhibiting relatively strong negative correlations [108]. The inference being that the water-soluble metals associated with PM_{10} were primarily responsible for the oxidative potential and plasmid DNA damage. A better understanding of the mechanisms that lead to toxicity can help in developing better in vitro models.

Biomonitoring

Biomonitoring (the measurement of a chemical or its metabolites in body tissues and fluids) data can improve our understanding of exposure. It can contribute to a multiple lines of evidence approach and allow a better understanding of how our bodies interact with the environment. Furthermore, biomonitoring studies have the potential to guide risk management decisions for all legacy mining communities into the future. The case for biomonitoring data in improved enforcement of health and safety legislation to protect both workers and the wider community against the hazards posed by mining activities is clear [77•].

Correlations between PTEs in household dust and children's hair, in two different environmental settings (mining district; suburban non-mining area), showed significantly higher indoor dust and hair concentrations of PTEs in the mining district [17]; a significant exposure-biomarker association was found, particularly for Pb. Socio-economic determinants related to unpaved roads and the physical environment of the households increased the exposure to PTEs by promoting dust accumulation indoors. Furthermore, a child's behaviour may be a modulating factor in the exposure to PTEs, as the correlation between Pb in dust and Pb in hair was stronger for children who played with dirt (soil) in the mining neighbourhood. Dust particulates adhering to clothing and shoes can easily be carried by the children into their home environment [17]. In villages surrounding the Huodehong lead-zinc mine, women showed significantly ($p < 0.01$) higher hair contents than men for the same PTEs, probably due to differences in individual exposure frequencies and exposure characteristics, metabolism, and physiology [101] (cf. Fig. 1).

Determinants of Disease in Mining Communities

Mining, like any industry or exposure, has its share of diseases specifically related to the type of mine, the particular industrial processes and the workforce connected to each mine. The role of metalliferous mine dust in the aetiology of these diseases needs to be seen in relation to a broad view of possible determinants of disease: individual, social, economic and environmental factors which may interact as they impact people's health [64]. These determinants operate on scales ranging from the individual (e.g. sex, age, genetics) to the international (e.g. policies and regulations). For example, the development of pneumoconiosis among miners depends on the chemical composition of dust, fineness of dust, air concentration of dust, but also length of period of exposure and underlying health status of the exposed worker [46, 66]. We use three broad classes of determinants (occupational, environmental, human and societal) to illustrate the complex interplay of considerations and issues that influence disease (Fig. 1).

Occupationally Related Determinants

The mining industry is known for its highly risky and hazardous working environment. Occupational hazards relevant to disease associated with metalliferous mine dusts include the following:

Chemical The unrestricted use of metals can lead to high levels of exposure to a range of PTEs. For example, the use of elemental mercury in small-scale artisanal gold mining leads to methyl-mercury pollution of the local environment and ingestion through the locally grown diet. Inhalation of elemental Hg by the children and other workers, often working in kitchens away from the actual mine, is an issue [14].

Environmental Adverse environmental conditions such as absence of natural light, fresh air, and high dust volumes contribute to mental stress and ill health as well as diseases specific to the dust characteristics and metal content.

Social and Managerial Risks Managers' attitudes to safety and miners' roles affect health outcomes [52, 114]. Psychological stress levels in Australian miners were higher than in non-mine workers, with alcohol use, work role (as managers), level of work satisfaction, financial factors and job insecurity contributing factors. Added to this was a perception of lower workplace support for people with mental health problems [29••].

Personal The interaction of psychological stress with exposure to traffic PM is synergistic [5•]. It can be expected that mining dust acts similarly when added to psychological stress. Age and sex affect health, with children and women showing different vulnerabilities from men due to different biochemical and physiological characteristics. Miners in regulated industry are usually adults between school leaving age and retirement, with men more likely in many countries to be working at the mine face and women in less physically demanding posts, each with differing exposures to toxins and other disease determinants. Older miners are likely to have longer exposures to dust and toxins. In artisanal and small-scale mining, children are found working directly in the mines, or more likely in the recovery processes; for example, exposed to Hg in the amalgamation process in gold extraction.

Environmental Determinants

Wider Environmental Quality Pollution of water, soil, or air by PM of the wider inhabited area around a mine can affect the local food sources and hence diet, with immediate and long-term effects [1•].

Living Condition Deprivation is a major determinant of ill health. Mining wastes, the poor and deprived, and the most vulnerable members of the community are often found in juxtaposition.

Exposed communities commonly comprise historically marginalised ethnic groups living in informal settlements, state, or Government-supported housing and retirement homes (e.g. [64]). Living near a mine and spoil or a metal-emitting industry put people at risk of exposure to PM and associated metals ('neighbourhood exposure') [35]. Elderly people exposed to mining waste, which is often open to being spread widely by wind and rain, suffer a disproportionate burden of lung diseases [78•]. Family and friends can be exposed ('bystander exposure') to dust brought home on clothes, and develop related diseases including Pb poisoning or lung cancer.

Human and Societal Determinants

Individual Characteristics and Inheritance (e.g. Genetic) Gender, age and genetic inheritance contribute to vulnerability to the effects of exposure to environmental pollutants. Children's unique physiology, development and behaviour can influence the extent of their exposure [13]. Children are not small adults; they differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals, sometimes more, sometimes less. It is unlikely that a set of genes exist which give an easy molecular signature for toxicity to metals or other mined commodities. Nevertheless, genetic diversity clearly modifies the body's response to various exposures, even if the evidence is not detailed. Specific genes have been associated with coal workers' pneumoconiosis susceptibility [66], or protection [46] in a Chinese population, and decreased lung function in smokers living in the vicinity of Indian coal mines [34]. However, distinguishing between genes, epigenetic switches and socio-economic status ("nature and nurture") can be difficult and will take much more work: developing the exposome should help.

Personal and Lifestyle Choice Smoking can increase susceptibility to silicosis in miners [102], whilst nutritional status enhances or reduces the absorption of metals following exposure. For example, poor nutrition increases Pb absorption and toxicity [73]. Employment and housing in or near mines or places affected by metalliferous dusts may reflect lifestyle choices or the lack of them, easily compounded by related deprivation and socio-economic issues.

Health Care The level of emergency medical services infrastructure and preparedness differs significantly between countries [37]. Furthermore, non-emergency health care, where available, is typically focused on treatment, when a more fundamental need is prevention.

Social Capital Family and friends and the culture of the home community can put implicit or explicit pressure on workers to keep earning despite poor working conditions, and poor health, thus increasing exposure to dust and toxins, while adding to stress. In contrast, social mobilisation can drive positive changes and good social support is health protective [70].

Education Education affects health in the long term, at the individual, community and wider society levels, through complex personal and social interactions [113••]. Education can improve health through a multitude of channels: greater ability to access information and services, proficiency to navigate bureaucracies, greater political participation and voice [60•]. Many miners suffer a lack of education, which limits their job prospects, pushing them into artisanal mining and trapping them in poverty [104].

National and International Context In many ways, the global economy /trade has the biggest impact on health from mining given its influence on the 'safety climate' [37]. Furthermore, national health and safety regulations may exist, but be poorly complied with, often due to (global) economics. Mines that followed the US Mine Safety and Health Administration (MSHA) guidelines were less likely to report lung disease [112]. The dynamics of human populations in mining communities also has a role to play, such as the length of time spent in the affected area, nature of community infrastructure, i.e. old productive versus new and transient mining activity.

Health Outcomes and Response

Ill health may be visualised as a pyramid (dimension (scale) of the disease burden, Fig. 1 innermost circle) with decreasing numbers from those at risk of exposure to those who die. The number of people dying is easier to ascertain than the number of those exposed, although apportioning a cause of death to specific disorders and pathological processes can be tricky [3].

There is increasing evidence of a link between environmental pollution and preventable diseases, especially in developing countries. A comprehensive review of published epidemiological literature investigating environmental chemical exposure in Thai children concluded that exposure to PTEs (including As, Pb, Cd) in industrial and mining areas is one of three main types of chemical exposure, together with pesticides and air pollution. Major health outcomes included detrimental effects on cognitive function and cancer risk. Furthermore, the authors pointed out increasing concern, but little acknowledgment, about the effects of chronic mining-related exposure to PTEs such as As [91].

Exposure to PM can initiate or enhance disease in humans. With respect to cancers, then Cr, Ni and As are known carcinogens, whilst the evidence is less clear for Pb and Fe (cf. Table 2) [12, 84••, 105]. The consensus on Pb is that given its ubiquitous occurrence and many different forms it is hard to categorically evaluate its ability to cause cancer. The IARC [51••] list Pb as 'possibly carcinogenic to humans' (IARC group 2B), inorganic Pb compounds as 'probably carcinogenic to humans' (IARC group 2A) and organic Pb compounds as 'not classifiable as to

Table 2 Toxicology of common metal(oid)s in metalliferous mine dust and human carcinogenic status (IARC group)

Metal	Exposure route	Affected organs/systems	Health effects	Human carcinogenic status, IARC group*	Source
Arsenic (As)	Inhalation, ingestion, skin contact.	Skin, digestive system, liver, nervous system, respiratory system (nose to lung).	Inorganic As: skin 'warts' and skin cancer (from ingested As). May interfere with normal fetal development. Organic As: less toxic but little human information. Diarrhoea and urinary problems in animals.	Inorganic As known carcinogen (liver, bladder, lungs, skin) (group 1).	ATSDR, IARC, PHE
Cadmium (Cd)	Absorption from inhalation more effective than ingestion: 5–50% inhaled Cd absorbed through lungs; 1–10% of food and water Cd ingested—Fe lack increases Cd absorption. Dermal absorption almost non-existent.	Digestive system + liver, nervous system, reproductive system, kidneys, cardiovascular system, upper respiratory tract. Developmental toxin (known in animals)?	High concentrations irritant to stomach: vomiting and diarrhoea, occasional death. Inhaling chronic high concentrations damages lungs and can kill. Chronic inhalation of lower concentrations damages kidneys; can lead to osteoporosis and osteomalacia.	Cd and compounds known carcinogen (group 1).	ATSDR, IARC, PHE
Chromium (Cr)	Uptake depends on valency (III or VI) and solubility of Cr compound: ~ 0.5–1% Cr(III) in normal diet adsorbed in gastrointestinal tract. Cr(VI) more readily absorbed by both inhalation and ingestion. Insoluble inhaled particles remain in lung for long time.	Respiratory tract, cardiovascular system, gastrointestinal system, liver, kidneys, skin.	Cr(VI) more toxic than Cr(III), but Cr(VI) unstable in body, rapidly reduced to Cr(V), Cr(IV) and ultimately to Cr(III) by endogenous reducing agents. Acute ingestion of large amounts Cr(VI) can give severe respiratory, cardiovascular, gastrointestinal, hepatic, renal damage and may kill. Chronic inhalation of Cr(III) salts gives respiratory inflammation. Cr(VI) may cause occupational asthma, nasal septum ulceration and perforation, respiratory irritation, lung cancer and possible renal effects. Dermal contact in Cr-sensitised individuals can give allergic dermatitis; chronic dermal exposure can give deep skin ulcers.	Cr(VI) mutagenic; known carcinogen (group 1); Cr(III) not classifiable.	ATSDR, IARC, PHE
Cobalt (Co)	Inhalation: 50% inhaled dose absorbed for particles with geometric mean diameter 0.8 μm; ~ 75% for particles with geometric mean diameter of 1.7 μm. Co particles deposited in respiratory tract absorbed into blood after dissolution or transported back up to throat by cilia, then swallowed. Ingestion (probably < 50% absorbed). Skin contact: absorption through intact skin < 1%; through	Respiratory, cardiovascular, hepatic, renal systems and thyroid. Almost ½ of original lung burden persisted 6 months after exposure; elimination half-time for Co in human lung increased with time after exposure. Health effects of ^{60}Co not specific to Co, but apply to any radionuclide delivering the same beta and gamma radiation dose at a	Inhalation: the rare hard metal (lung) disease possible but evidence not conclusive. Respiratory effects (including asthma and fibrosis) depend on dose and chronicity. Heart, thyroid disease and decreased body weight. Ingestion: nausea, vomiting, diarrhoea. Increased number of red blood cells, possibly hæmoglobin. Allergic dermatitis possible.	Co and Co compounds possibly carcinogenic (group 2B). Cobalt metal with tungsten carbide probably carcinogenic (group 2B) but not clear if Co or W or together.	ATSDR, IARC

Table 2 (continued)

Metal	Exposure route	Affected organs/systems	Health effects	Human carcinogenic status, IARC group*	Source
	abraded skin almost 80% 3 h after exposure. Radioactive Co (primarily ^{60}Co) acts through skin contact—beta or gamma producers. ^{60}Co gamma rays commonly used for human radiotherapy.	comparable dose rate	Skin contact: local allergic reaction to Co metal but not salts. Mutually enhances Ni skin sensitisation.		
Copper (Cu)	Inhalation, ingestion, skin contact	Lungs, gastrointestinal tract, kidneys, liver, blood, skin, eye.	Inhalation: metal fume fever (cough, sore throat, tight chest, headaches, fever, muscle pains) from intense inhalation, lasts 1–4 days with no long-lasting effects. Ingestion: stomach pain, nausea, vomiting diarrhoea. Skin contact: inflammation, burns. Fragments can cause severe eye injury. Chronic exposure usually limited to specific, susceptible people.	Not listed by IARC. Inadequate evidence for a direct role in the development of cancer in humans.	PHE, [79]
Iron (Fe)	Ingestion. Healthy adults absorb 2–10% dietary load; if adult or child iron deficient, 80–90% absorbed through gut. Organic (heme) Fe more easily absorbed than inorganic (insoluble) salts. Inhalation.	Pituitary, thyroid, heart, liver, pancreas, gonads from ingestion. Lungs from inhalation.	5 stages of acute poisoning (ingestion): 1 gastrointestinal effects, 30 min–1 h; 2 quiescence, to 4 h; 3 shock, multi-organ failure, 2–24 h; 4 liver toxicity 12–24 h; 5 gut obstruction 1–7 weeks. Death. Chronic poisoning: excess Fe in many organs (haemochromatosis), giving diabetes, cirrhosis, heart disease, impotence, female infertility, premature menopause, death. Inhalation gives 'welder's lung' (siderosis) and lung cancer.	Organic (heme) Fe potential carcinogen but details unclear. Occupational exposure classified as group 1 carcinogen (iron, steel founding; haematite underground mining with exposure to radon). Ferric oxide and haematite group 3.	IARC, [, 39, 68]
Lead (Pb)	Inhalation (occupational): 30–50% inhaled particles deposited in lungs. Ingestion (general public): adults absorb 5–15%; in fasting conditions up to 45% absorbed; children absorb up to 53%. Skin absorption usually low.	Brain, circulatory system, genitourinary system; stored in bone and soft tissues.	Very high acute dose: gut disturbances, encephalitis, other effects on central nervous system, renal function, and blood. Chronic exposure most important: cognitive impairment in children, elevated blood pressure, renal toxicity, anaemia, reduced fertility, adverse birth outcomes. No threshold to toxicity (no safe dose).	Inorganic Pb probably carcinogenic (group 2A).	ATSDR, IARC, PHE, WHO
Mercury (Hg)	Inhalation: Hg vapour 80% absorbed; inorganic salts not absorbed well; organic salts easily absorbed. Ingestion: < 0.01% elemental Hg absorbed; usually < 10% inorganic	Distributed to all tissues but mainly accumulates in the kidneys; elemental Hg readily crosses into the brain	Acute exposure: inhalation (elemental Hg) may cause respiratory, central nervous system and cardiovascular effects, renal damage and gastrointestinal disturbances. Ingestion (inorganic Hg salts) may affect the	Metallic and inorganic Hg not classifiable as to carcinogenicity to humans; CH_3Hg possibly carcinogenic to humans.	ATSDR, IARC, PHE

Table 2 (continued)

Metal	Exposure route	Affected organs/systems	Health effects	Human carcinogenic status, IARC group*	Source
	salts absorbed (occasionally 40%). CH_3Hg well (95%) absorbed. Skin absorption least effective for metallic and inorganic Hg. $(CH_3)_2Hg$ rapidly absorbed through skin		digestive tract, and damage kidneys, cardiovascular system and skin/eye. Chronic exposure: inhalation of elemental Hg vapour may cause neurotoxicity, nephrotoxicity and affect mouth. Ingestion of inorganic Hg compounds may cause neurotoxicity, digestive tract effects and renal failure.		
Nickel (Ni)	Inhalation and ingestion.	Digestive system, nose, genitourinary system.	Acute exposure: gut upset, headache. Nickel carbonyl most toxic nickel compound from acute inhalation. Chronic inhalation of Ni or compounds: rhinitis, sinusitis, anosmia (no smell); in extreme cases perforation of the nasal septum. Ni carbonyl and soluble salts considered reproductive toxicants.	Ni compounds known carcinogen (group 1). Elemental Ni possibly carcinogenic (group 2B).	ATSDR, IARC, PHE
Uranium (U)	Radiation (outside and inside body): percentage by radioactivity: ^{234}U 49, ^{235}U 2, ^{238}U 49; percentage by mass ^{234}U 0.006, ^{235}U 0.7, ^{238}U 99.3. Inhalation: particles largely remain in lungs (0.8–5% U absorbed). Ingested soluble particles only slightly absorbed (0.1–6%). Very little absorbed through skin.	10% into kidneys but quickly lost; by 3 months only 0.1% initial dose into blood; 15% into bone with slow release to ~ 1% at 25 years. Bone marrow.	65% excreted first day, another 10% by end of first week; continuing slow excretion (0.002% initial dose at 1 year). Renal failure due to heavy metal toxicity. Radiation leukaemia less common than chemical toxicity.	Radiation carcinogenic; risk generally assumed proportional to radiation dose. May or may not be threshold of effect. Limited human evidence for chemical carcinogenicity of mixed isotopes; sufficient animal evidence for carcinogenicity of ^{233}U, ^{234}U, ^{235}U, ^{238}U. Not classified by IARC.	ATSDR, IARC, PHE
Zinc (Zn)	Inhalation; ingestion: under normal physiological conditions, 20–30% of ingested zinc is absorbed; skin absorption occurs.	Respiratory system, gastrointestinal tract, haematological system.	Toxicity low. Metal fume fever (cough, sore throat, tight chest, headaches, fever) from intense inhalation of ZnO (smelting; welding) lasts 1–4 days with no long-lasting effects. ZnCl in smoke bombs most irritating salt in lungs and on skin. ZnO not irritating to skin. Chronic ingestion may lead to anaemia.	Not listed by IARC. Probably protective.	ATSDR, [56]

ATSDR, Agency for Toxic Substances and Disease Registry (USA); IARC, International Agency for Research into Cancer; PHE, Public Health England; WHO, World Health Organisation

*IARC groups:

Group 1 Carcinogenic to humans (120 agents)

Group 2A
Probably carcinogenic to humans (82 agents)

Group 2B Possibly carcinogenic to humans (302 agents)

Group 3 Not classifiable as to its carcinogenicity to humans (501 agents)

Group 4 Probably not carcinogenic to humans (1 agent)

its carcinogenicity to humans' (IARC group 3), but may be metabolised to ionic, inorganic lead and so become 2A (Table 2). Mining, however, can lead to an increased risk of contracting other diseases: increased pulmonary tuberculosis has been recorded in underground Cu miners in Zambia [76]. A high prevalence of wheeze (a symptom of asthma) and rhinoconjunctivitis has been noted among the elderly in communities located near mine dumps [78•]. Significantly increased risk of larynx cancer has been observed for many production and transport professions, including miners [15], possibly related to PM exposure.

Whilst an epidemiological association has been demonstrated between mortality and morbidity in lung cancer and cardiovascular diseases and exposure to PM the actual mechanisms of this relationship remain unclear. Chronic obstructive pulmonary disease (COPD), a slowly progressing disease characterised by a gradual loss of lung function, causes 4% of overall global disease burden [41••]. The most important risk factor is active smoking, but other risk factors are occupational or environmental (including coal and hard-rock mining), and socio-economic depravation in childhood [20].

Asthma, an inflammatory respiratory condition, is a major cause of disability, health care utilisation and reduced quality of life and accounts for approximately 1% of global overall disease burden [41••]. Inhaled PM induces oxidative stress leading to inflammatory responses in the airways and bronchial hyperreactivity and metal fumes are well-recognised causes of occupational asthma, but the contribution of metal dusts to non-occupational asthma is less obvious. High blood Pb is correlated with having asthma in children, but the meaning is unclear [107]. Other diseases linked to metal exposures (with or without air pollution) include chronic neurological disorders such as Parkinsonism and Alzheimer's disease (including Al, Cu, Mn,) [11•], renal and liver disorders (Table 2).

This multifactorial landscape generates a complex relationship between mining, metalliferous dusts and human health (Fig. 1). Differences in health outcomes occur both temporally and spatially and are overlain by differences in management of the hazard and in the extent of, and behaviours towards, regulatory compliance. Risk assessment and health and safety management are important elements of most industries, including mining, and have a significant role to play in reducing incidences of mining-related ill health. Risk management refers to all activities and procedures undertaken to manage the inherent risks of that particular industry. Risk management does not eliminate risk, but supports the identification of appropriate, and proportionate, strategies and control measures to manage them. Dust abatement strategies are the primary preventative measure and improved ventilation, more effective dust extraction systems, as well as water spraying systems have been linked to reduced incidences of mining-related diseases [55]. Regulatory limits are also important here, whilst safety organisations, workers' unions and senior managers also need to be active, not passive bystanders [114].

Current risk assessment guidance still principally focuses on a chemical-by-chemical approach, and have not kept pace with research into the possible synergistic or antagonistic toxicological effects of complex environmental mixtures [2]. A review of studies on the relationships between exposure to Pb, As and Cd and neurodevelopmental outcomes in prenatal and early childhood identified the synergistic effect of combined mixtures on health outcomes [95]. There is also a need to build non-chemical stressors into our risk assessment models. Parallels can be drawn with air pollution studies where combined exposure to psychosocial stress and particulate air pollution has been shown to be worse than exposure to either alone [5•]. However, we acknowledge that there are chemical and physical differences between metalliferous mine dusts and traffic sourced PMs and so we need to be cautious about what can be safely inferred from traffic PM-related research.

Exposure to metalliferous dusts remains a significant environmental health concern, especially in many low- and middle-income countries where dust emitting industries are often less well regulated [60•]. Whilst occupational exposure to metalliferous dust has long been recognised as potentially hazardous to workers health, community-wide interventions to protect vulnerable communities, including integrating biomonitoring and surveillance (e.g. miners' lung function) into existing health programs and surveys, need to be promoted alongside local and national-level environmental control policies [60•]. Arquette et al. [8] describe a community defined risk assessment and risk management model, emphasising the important contribution Native people can bring in terms of traditional, cultural and ecologic knowledge of their environment. Semi-qualitative and qualitative research is also important for assessing and better targeting individuals' and at-risk subgroups risk perceptions and behaviours [45].

Future risk assessment approaches should strive to identify and integrate the effects of exposure to complex chemical mixtures, non-chemical stressors (such as socio-economic and cultural drivers), alongside individual differences (e.g. genetic variability). We are still a long way from a regulatory environment that drives the development of risk assessment methods that consider the breadth of potential stressors. The complex interplay of advances in scientific and technological capability, with economic and political drivers, all play a part, but a fuller commentary on this is beyond the scope of this review.

Conclusions

Research linking environment to human health is starting to mature, highlighting the subtlety of multiple exposures, mixtures of substances and the cumulative legacy effects of life in disrupted and stressed environments. We are developing more

refined biomarkers of these responses which enhance our appreciation of the burden of effects on society and also direct us to more sophisticated investigation of risk assessment processes. Yet, the disparity of the global geography of disease burden remains a challenge. Combating environmental hazards has remained a major area of concern for the UN Sustainable Development Goals (SDGs, [98]). Despite ~25% of global disease burden being related to environmental factors [], identifying health impacts from exposure to chronic/acute hazards from dust and understanding the complex relationship remains challenging. How we utilise and interact with our environment adds another layer of complexity. Academics could do more to develop evidence-based solutions to promote relevant preventive activities to issues around the sustainable extraction and use of mineral resources, working in partnership with government, industry and communities, at local, national and international scales [60•]. The development of a shared understanding of the research gaps, information access, and the needs of stakeholder/user communities, together with the enablers and challenges, is vital to address local to global health and wellbeing challenges arising from environmental pollution, such as from mining- and mine-related metalliferous dusts. Research at the environment-health nexus has traditionally been viewed as too environmental for funding bodies in the geosciences, yet too environmentally focussed for health organisations and related charitable funders. We need to tackle this deficit if we are to embrace the 2030 Agenda for Sustainable Development and achieve the UN SDG of good health and wellbeing.

Compliance with Ethical Standards

Conflict of Interest Jane A. Entwistle, Andrew S. Hursthouse, Paula A. Marinho Reis, Alex G. Stewart declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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