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METALS-INDUCED PULMONARY FIBROSIS

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Abstract

Purpose of review: The incidence of pulmonary fibrosis is increasing worldwide and may, in part, be due to occupational and environmental exposures. Secondary fibrotic interstitial lung diseases may be mistaken for idiopathic pulmonary fibrosis with important implications for both disease management and prognosis. The purpose of this review is to shed light on possible underlying causes of interstitial pulmonary fibrosis and to encourage dialogue on the importance of acquiring a thorough patient history of occupational and environmental exposures.

Recent findings: A recent appreciation for various occupational and environmental metals inducing both antigen-specific immune reactions in the lung and nonspecific “innate” immune system responses has emerged and with it a growing awareness of the potential hazards to the lung caused by low-level metal exposures. Advancements in the contrast and quality of High Resolution CT scans and identification of histopathological patterns of interstitial pulmonary fibrosis have improved clinical diagnostics, and recent findings indicate specific hotspots of pulmonary fibrosis within the US. Increased prevalence of lung disease in these areas appears to be linked to occupational/environmental metal exposure and ethnic susceptibility/vulnerability.

Summary: A systematic overview of possible occupational and environmental metals causing interstitial pulmonary fibrosis and a detailed evaluation of vulnerable/susceptible populations may facilitate a broader understanding of potential underlying causes and highlight risks of disease predisposition.

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Conflict of Interest

The authors declare that they have no conflict of interest

Human and Animal Rights and Informed Consent

All procedures performed in cited studies involving human participants conducted by the authors were in accordance with the ethical standards of the University of New Mexico Institutional Review Board. Animal studies performed by the authors were performed in accordance with the Animal Care and Use Committee.

Keywords

Pulmonary fibrosis; interstitial lung disease; metals; environmental health; occupational exposure; health disparities

Introduction

Metal particles, dusts, and/or fumes deposited in the lung by inhalation or ingestion may give rise to pulmonary fibrosis and functional impairment, depending on the fibrogenic potential of the agent and on poorly understood host factors [1]. The fibrogenic potential is presumably determined by the ability to interfere with the pulmonary immune-inflammatory system, either directly via effects on alveolar macrophages, or indirectly via injury to epithelial cells [1]. As in other forms of interstitial lung diseases, the fibrotic process is likely dependent on the occurrence of alveolitis with an abnormal release of immune response mediators. The exact pathogenic mechanisms of metals-induced pulmonary fibrosis have not been elucidated despite continued research efforts. Within the conceptual framework that continued pulmonary injury and/or inflammation ultimately lead to fibrosis, metal-related interstitial lung diseases may be divided into several broad categories: 1) diffuse fibrotic interstitial lung diseases, often described in patients exposed to uranium and arsenic; 2) benign pneumoconiosis with little or no fibrosis such as siderosis which results from the inhalation of iron compounds; 3) sarcoid-like or hypersensitivity pneumonitis-like epithelioid granulomatous lung diseases reported with beryllium, aluminum, and titanium exposure; 4) giant cell and desquamative interstitial pneumonitis observed in workers exposed to cobalt and tungsten; and 5) acute chemical pneumonitis in the case of aluminum, cadmium and nickel exposure. This review will primarily focus on diffuse interstitial pulmonary fibrosis, which is often misdiagnosed as ‘idiopathic’ pulmonary fibrosis in the absence of an adequate occupational and environmental history.

Idiopathic pulmonary fibrosis (IPF), the most common and the most severe form of the idiopathic interstitial pneumonias, is characterized by progressive accumulation of collagen/fibrotic tissue in the lung parenchyma [2]. IPF can be diagnosed by the presence of a usual interstitial pneumonia (UIP) pattern on a high-resolution chest CT scan (HRCT) or by specific combinations of radiologic and histopathologic patterns from a surgical lung biopsy [2]. Any “secondary” causes of interstitial fibrosis should be carefully excluded to make this clinical diagnosis. In addition to cigarette smoking, environmental and occupational factors have been documented as known risk factors for IPF, including metal dust exposure [3], however it is plausible that metals-induced pulmonary fibrosis is truly a unique disease and not classifiable as “idiopathic”. There is a global rise in the incidence of IPF [4] as well as an increase in IPF-induced mortality in the European Union over the last two decades [5], whether this increase is due to idiopathic disease or due to the global increase in secondary pulmonary fibrosis (such as from air pollution or metal dust exposure) is unknown. Moreover, mortality rates from interstitial lung disease and pulmonary sarcoidosis have substantially increased in the United States from 1980 to 2014 (Figure 1A) with a distinct localization in the southwestern United States [6], an area harboring thousands of abandoned hard-rock mining sites. Advances in IPF therapy with emerging antifibrotic medications [7]

may open the door for future research in applying those therapeutic options to secondary pulmonary fibrosis including metals-induced pulmonary fibrosis.

This review discusses reports from both human and animal studies investigating the link between occupational and environmental metal exposures and pulmonary fibrosis (Summary of findings Figure 1B). Increased susceptibility and vulnerability within specific populations will be also explored. While occupational exposures allow researchers and clinicians to investigate metals-induced pulmonary outcomes at the epidemiological level, there are very few explicit animal models of IPF. The *in vivo* models involving metal-based exposures that have been studied have focused primarily on proinflammatory endpoints, collagen deposition in the lungs, oxidative stress markers and histopathological changes. *In vitro* models offering toxicity assessments can also be found throughout the literature often utilizing cell lines such as fibroblasts, macrophages and lung epithelial cells. To this end, gaps in knowledge with regard to metals-based pulmonary research will be discussed.

Aluminum

Aluminum hydroxides and oxides are used in products ranging from food additives and pharmaceuticals to abrasives, ceramics, and fire retardants. Aluminum use and primary aluminum production results in the generation of airborne particles, fumes, gasses, and materials with the potential for inducing work-related asthma and various phenotypes of interstitial lung disease, including usual interstitial pneumonitis-like pattern [8–11], pulmonary nodulofibrosis with immune mediated interstitial granulomatous inflammation known as aluminosis [12–14], desquamative interstitial pneumonitis [15], and pulmonary alveolar proteinosis [16]. It was previously believed that aluminum-related pulmonary fibrosis was rare with most case reports prior to the 1980 era [9]. However, a 1988 study reported that up to 8% of workers in an aluminum production company, where bauxite was mined and refined and alumina-based chemicals were produced, had small irregular opacities involving the middle and lower lung zones with virtually no rounded opacities (a radiologic picture consistent with the usual interstitial pneumonitis phenotype) [17]. Moreover, disease prevalence was increased among cigarette smokers indicating a joint effect of smoking and occupational exposure [17]. In a case report with pathological confirmation, Gilks et al. demonstrated upper lobe involvement by usual interstitial pneumonitis-like disease, indicating that this phenotype may affect all lung zones. [9]. On the other hand, a recent cross-sectional study of workers from an aluminum powder industrial plant detected parenchymal changes using HRCT in 24% of the high-exposed workers, almost entirely of the upper lobe predominant nodulofibrotic variety consistent with the aluminosis phenotype [12]. It is possible that the differentiation of the phenotype of interstitial lung disease in aluminum exposed workers may depend upon the type of aluminum exposure, the presence of concomitant exposures such as silica and smoking, and unknown host factors.

Few controlled exposure studies of aluminum have been conducted to explore the potency and mechanisms underlying fibrotic outcomes. A high dose aluminum hydroxide instillation exposure resulted in compromised pulmonary function in rats, consistent with fibrotic disease, but over a subacute time frame and without supporting histology to infer a fibrotic

process [18]. In a subsequent study, pure alumina (Al-P) or aluminum foundry (Al-F), found in aluminum dust, was intratracheally instilled into rats and biomarkers were assessed 3, 6 and 9 months following the exposure. [19]. Al-F dust induced marked changes in epithelial cells and enhanced remodeling of collagen deposition and elastase fibers at 6 and 9 months. Additionally, bronchoalveolar lavage fluid (BALF) demonstrated an increase in total cells, especially a late (9 month) surge in neutrophils for both particle types. Elevations in matrix metalloproteinases were also noted. An additional source of aluminum exposure has emerged for workers involved in the manufacturing of engineered nanomaterials, including multiwalled carbon nanotubes (MWCNTs). Aluminum oxide coatings are frequently applied to enhance the functional properties of MWCNTs [20]. In an in vitro study, Al₂O₃-coated MWCNTs were incubated with Tamm-Horsfall Protein 1 (THP-1) and macrophages or human peripheral blood mononuclear cells (PBMC) and cell supernatants assayed for cytokines. This particulate exposure resulted in significantly upregulated interleukin (IL)-1 β , yet reduced protein levels of IL-6, and tumor necrosis factor (TNF)- α in THP-1 cells. Ultimately, however, aluminum has not been studied extensively from the standpoint of fibrosis-like disease.

Arsenic

While most metal-associated lung fibrosis arises due to inhalation of specific metals as dusts or fumes, arsenic may also contribute to lung disease through systemic uptake. A recent meta-analysis of 9 studies identified a strong, inverse link between lung function and arsenic intake, specifically noting the likelihood for development of a restrictive phenotype [21]. Residents of many parts of the world, particularly in India, Bangladesh, Taiwan, and Northern China ingest drinking water contaminated with arsenic and are at risk for arsenicosis, a multisystem disorder [22]. Respiratory manifestations of arsenicosis include not only pulmonary fibrosis but also chronic bronchitis and emphysema phenotypes of COPD, bronchiectasis, and secondary pulmonary hypertension [22]. Given the presence of multiple concomitant lung diseases causing similar respiratory symptoms and decline in spirometric parameters, the prevalence of pulmonary fibrosis in epidemiological studies is difficult to estimate.

Pulmonary fibrosis was first described with chronic ingestion of arsenic by drinking contaminated water in Chilean children as early as the seventies. Rosenberg conducted autopsies on five infants manifesting characteristic features of chronic arsenic toxicity, including skin pigmentation and/or keratosis [23]. Lung tissue was examined in four of the five infants, with abnormalities found in each and two having pulmonary fibrosis with mild bronchiectasis [23]. Symptoms of chronic lung disease, most commonly cough, were present in 57% of 156 cases of chronic arsenic toxicity in a 1995 study in West Bengal, India [24]. In a cross-sectional epidemiological study of 6,864 nonsmokers in West Bengal, men and women with arsenic-associated skin lesions demonstrated significantly higher odds separately for cough, shortness of breath, and abnormal lung sounds on auscultation (crepitations and/or rhonchi) than those with normal skin [25]. In another study, a 100 mcg/L higher level of arsenic in drinking water was associated with a 41 mL lower mean forced vital capacity (FVC) and 45 mL lower mean forced expiratory volume in one second (FEV₁) value in men [26]. In another study in West Bengal, the distribution of abnormal

spirometric patterns found in cases with chronic arsenic poisoning was obstructive (69%), purely restrictive (4%) and mixed obstructive plus restrictive (28%), with a worsening correlation of lung function with increasing degree of arsenic toxicity [27]. BALF samples of those with arsenic-related lung involvement demonstrated higher levels of inflammation than those without [27]. In a hospital-based study of 29 cases of chronic arsenic toxicity with nonmalignant lung disease in West Bengal, a diagnosis of interstitial lung disease, based on clinical evaluation, chest x-ray and in limited cases HRCT scans, was made in 9 cases [27]. In this study, COPD was the most commonly diagnosed lung disease whereas in a larger population-based study, bronchiectasis was the most commonly diagnosed lung disease on CT scans [28].

With regard to animal studies, arsenic exposure routes via ingestion and drinking water have been thoroughly investigated [29–32], however there are limited studies involving inhaled arsenic and subsequent respiratory and pulmonary pathology. In one study, a two-week, *in vivo* inhalation exposure to arsenic-containing dust resulted in oxidative DNA damage and apoptotic cell death in the lung [33]. This effect was mitigated using a sulforaphane intervention with subsequent activation of nuclear factor-like 2 (Nrf2) and decreased inflammatory cytokine production. In another study, two-weeks of inhaled arsenic trioxide exposure resulted in high, detectable concentrations of arsenic in the lung, blood and spleen, with minimal concentrations in the brain [34]. Interaction with other toxicants has also been documented in the literature. Following a 28-day exposure to aerosolized arsenic compounds (3.2 mg/m^3 for 30 min) and cigarette smoke (5 mg/m^3), DNA oxidation was significantly elevated and total glutathione levels were decreased compared to arsenic or cigarette smoke exposure alone [35]. Additionally, 8-Oxo-dG, a marker of DNA oxidation was present in the nuclei of airway epithelium and sub-adjacent interstitial cells. A similar exposure model noted exacerbated remodeling of an emphysematous phenotype when mice were concomitantly exposed to tobacco smoke and arsenic, albeit via oral gavage [32]. Interestingly, a 6-week oral ingestion exposure to arsenic led to changes in the lung protein expression and genomics, providing biological plausibility and mechanistic insight as to how ingested arsenic may impair lung homeostasis [29]. Though As_2O_3 particulates delivered intratracheally in rats were not retained in the lungs, instillation resulted in elevated lung dry weight, protein, DNA and collagen (4-hydroxyproline) content [36]. These data suggest an acute fibrogenic response following As_2O_3 exposure. Intratracheal instillation of GaAs (gadolinium-arsenic) particulates produced similar effects with significant elevations of lung lipids and proteins. At the end of the two-week study, 28% of the arsenic dose was retained in the lungs and 7% of the arsenic dose was detected in the blood. In areas of high arsenic contamination, high amounts of arsenic are retained in the blood, urine, feces and other tissues [37].

While high arsenic contamination is often seen in low income countries, exposure to arsenic may also occur in high income countries. This exposure is often from contaminated drinking water which is generally thought to be more harmful to human health than exposure to arsenic from contaminated foods, often grown in farms using arsenic pesticides or on soil with a previous history of arsenic pesticide use. In high income countries, the degree of arsenic exposure from contaminated drinking water is however substantially lower than in low-income countries and the association with lung disease is more difficult to prove. In a

small New England Lung Cancer Study, the geometric mean of toenail arsenic concentration of three patients with diagnosis of pulmonary fibrosis was not significantly different from the 455 subjects without pulmonary fibrosis [38].

Cadmium

Cadmium (Cd) is an environmental contaminant that is toxic, mutagenic and carcinogenic [39–41]. Inhalation is one of the main routes of environmental and occupational Cd exposure [42] and can occur during the production of nickel cadmium batteries and electroplating, as well as pigment and cadmium alloy manufacturing [43]. Cadmium is not only associated with inhalational fevers, acute chemical pneumonitis, chronic bronchitis, emphysema, and lung cancer, but also with pulmonary fibrosis [43]. In one small study, 29% of workers chronically exposed to high concentrations of airborne cadmium at a cadmium production plant showed interstitial fibrosis on chest radiographs [44]. A dose-response inverse association was observed between FVC and both average or maximal urinary cadmium concentration as well as months of work in cadmium fume areas [44]. Additionally, acute cadmium inhalation has been shown to provoke a long-term fibrotic response in the lungs in some cases studies [45].

In addition to human studies, the effects of pulmonary Cd exposure have been documented in several rodent studies [46–48]. Cadmium oxide nanoparticles, which comprise optoelectronic devices and are also used in pharmaceutical applications and medical imaging, have potential for inhalation exposure in an occupational setting [46]. Levels of total protein, lactate dehydrogenase activity, cytokine markers of inflammation including IL-1B, TNF- α , interferon (IF) γ , matrix metalloproteinase (MMP)-2 and MMP-9 increased after inhaled exposure to cadmium oxide nanoparticles. Following inhalation, MMP-2 decreased to control levels and MMP-9 remained significantly elevated 7 days post-exposure. Additionally, histopathological lung sections revealed fluid and inflammatory cell infiltration in addition to septum wall thickening and increased bronchus-associated lymphoid tissue. Cadmium chloride inhalation resulted in significant DNA damage as determined by a Comet assay in a CD-1 mouse model [48]. Intratracheal instillation of cadmium chloride resulted in increases in BAL lactate dehydrogenase (LDH), total protein, N-acetyl- β -d-glucosaminidase (NAG), and total inflammatory cells. At all cadmium chloride doses (25, 100, 400 μ g/kg body weight) pulmonary fibrosis as per trichrome stain was present [47]. In this study, alveolar macrophage fibronectin release with pulmonary fibrosis mirrored the development of interstitial lung disease and was suggestive of an early indicator of fibrosis.

Copper

Copper dust and fumes are inhaled during its mining, smelting, refining and welding. Inhalation of copper dusts and fumes may result in metal fume fever, nasal ulceration, respiratory tract irritation, and airflow obstruction [43, 49]. The use of copper sulfate solution to combat mildew in vineyards is associated with granulomatous lung disease or Vineyard sprayer's lung [50] and progressive massive fibrosis may be seen [49]. While the potential role of copper exposure in fibrotic interstitial lung disease is not well established in

humans, a recent animal study investigating adverse lung-related outcomes following exposure to copper nanoparticles indicates a possible role of copper exposure in fibrosis. Lai et al. demonstrated induced pulmonary toxicity and fibrosis following intranasal exposure of C57BL/6 mice to copper oxide nanoparticles [51]. This exposure was followed by epithelial apoptosis as determined by TUNEL staining, flow cytometry and western blot analysis. An increase in reactive oxygen species (ROS) resulted in expression of progressive fibrosis marker α -SMA, suggesting that copper oxide nanoparticle exposure may be responsible for pulmonary fibrosis induction. An additional study of copper nanoparticle inhalation reported increased recruitment of total cells and neutrophils to the lungs as well as increased total protein and LDH activity in BALF relative to controls [52]. However, an earlier study reported that while whole-body inhalation of copper nanoparticles significantly elevated BALF cytokines and resulted in perivascularitis and alveolitis, micrographs of lung sections revealed no signs of fibrosis, peribronchiolitis or interstitial pneumonitis post-exposure [53]. Moreover, there was no visual evidence of phagocytosed copper nanoparticles engulfed by macrophages at 0 or 3 weeks post exposure. As such, research into the possible role of copper nanoparticles in adverse lung outcomes is minimal with varied results. Given the growing use of copper in nanoparticle production, this area of investigation may expand in the future.

Molybdenum

Molybdenum dust is produced during mining but the vast majority of molybdenum fume exposure occurs in metallurgical applications such as stainless steel and cast-iron alloy manufacturing [54]. It is currently unclear whether molybdenum-exposed workers are at risk for developing fibrotic interstitial lung disease. In one study of 43 exposed workers in a metal plant and 23 non-exposed control workers, chronic inhalation of molybdenum trioxide was not associated with radiological signs of interstitial lung disease or lung function abnormalities. However, analysis of bronchoalveolar lavage fluid from 33 symptomatic exposed workers demonstrated inflammatory changes consistent with subclinical alveolitis, as compared to 10 asymptomatic exposed workers or to 23 non-exposed control workers, indicating an adverse lung effect of chronic molybdenum inhalational exposure [55]. Moreover, exposure to molybdenum in the form of mixed-metals may be linked to adverse pulmonary health. Exposure to dust from cobalt chromium molybdenum (CoCrMo) alloys has recently been described to cause dental technician's pneumoconiosis, a dust-induced fibrotic lung disease. Thirty-seven dental technicians in central and south eastern Sweden with at least five years of exposure were evaluated [56]. Six subjects (16%) showed radiological evidence of pneumoconiosis. The lung function of the study group was reduced compared to historical reference material [56]. However, it is unclear whether this fibrotic interstitial lung disease is due to the approximately 60% cobalt, 30% chromium or the 5% molybdenum content of the alloy [57]. Few animal studies have been conducted with inhaled molybdenum. A National Toxicology Program report on molybdenum carcinogenicity in rats demonstrated alveolar inflammation at exceedingly high concentrations (100 mg/m³), but did not examine functional or molecular changes [58].

Tungsten and Cobalt

Hard metal or cemented tungsten carbide is found in tools used for high-speed cutting, drilling, grinding, or polishing of other metals or hard materials such as diamonds [1]. In addition to work-related asthma, hard metal workers develop hard metal lung disease, described in case reports/series to present with various pathological patterns, including hypersensitivity pneumonitis, obliterative bronchiolitis, nonspecific interstitial pneumonitis, giant cell interstitial pneumonitis, desquamative interstitial pneumonitis, and usual interstitial pneumonitis [59, 60]. In an epidemiological study of 319 exposed workers in a hard metal factory, three workers had diffuse shadows on their chest radiographs of significant profusion (of 1 or more), with one case suspected of having pulmonary fibrosis on a lung biopsy [60]. The UIP pattern typically presents in older workers with longer exposure duration, is considered the prominent feature in advanced lung disease, and is believed to be distinct from and not a progressive form of giant cell interstitial pneumonitis [59]. Although usually lower lobe predominant, upper lobe fibrosis has also been described [1, 61]. It is believed that tungsten carbide is not the agent responsible for the fibrosis but that it is more likely due to the binding agent cobalt [1]. Interestingly, when pure cobalt dust exposure was studied in a cross-sectional study of 82 workers in a cobalt refinery, no chest radiographic abnormalities were noted, even among those with symptoms of dyspnea and wheezing [62]. This finding is compatible with experimental studies indicating that interaction of other airborne pollutants with cobalt particles plays a part in the pathogenesis of parenchymal lung lesions in hard metal workers [62]. *In vitro* assays of cobalt-containing dusts in murine peritoneal and alveolar macrophages revealed significant increases of LDH release [63]. Similarly, *in vitro* treatment of isolated alveolar macrophages with a tungsten carbide cobalt mixture resulted in decreased glucose uptake and suppressed superoxide anion production [64].

Uranium

Uranium is a natural, radioactive heavy metal frequently used in nuclear applications. Different forms of uranium with specific isotopic compositions (natural, depleted and enriched) are present during various steps in the nuclear industry [65]. Depleted uranium is radioactive and often used in not only nuclear, but also military applications including heavy tank armor, armor-piercing bullets and missiles. Therefore, inhalation poses a major risk for industrial workers and military personnel. However, assessment of occupational uranium exposure on respiratory health can be difficult as uranium industry workers such as miners, millers and transporters are exposed to several other pollutants in addition to uranium, including silica, radon, and mixed dust. Uranium has radiotoxic and chemotaxis properties, both of which likely contribute to adverse respiratory health effects [66]. The two main target cells of inhaled uranium are airway macrophages and epithelial cells [67]. After exposure to the alveolar region, macrophages are involved in particle clearance and retention [68]. Inhaled uranium dust particle exposure in the lungs and tracheobronchial region results in neoplasia and fibrosis in humans [69], results that are in agreement with data reported following uranium exposure in a rat model [70]. In the latter study, DNA strand breaks in BAL cells and increased inflammatory cytokine expression in the lungs following inhalation of uranium were observed. Repeated inhalations also led to upregulation of hydroperoxide

levels, a measure of potential oxidative stress. *In vitro* uranium exposure in macrophages resulted in significant TNF- α secretion and MAP kinase activation [71].

There are significantly more studies on the adverse pulmonary effects of uranium in humans, with the majority of data originating from uranium miner cohorts. Previously, chest radiographic abnormalities were recognized as upper lobe predominant round opacities consistent with silicosis [72]. However, recent data from a New Mexico uranium workers cohort revealed that the most common chest radiographic abnormalities were lower lobe predominant small irregular abnormalities, mimicking the pattern seen in IPF [73]. Both obstructive and restrictive lung function abnormalities are described in subjects exposed to uranium, specifically uranium miners, and the type of abnormality may be explained by co-exposures or underlying genetic factors. In a cohort of New Mexico uranium miners, non-Hispanic white subjects showed more obstructive lung disease on spirometry, while a high prevalence of restrictive lung disease was observed among American Indian workers [74]. In an additional study from the Wismut miners' cohort, a high mortality from nonmalignant respiratory diseases including silicosis and pneumoconiosis was indicated. This mortality however was associated with cumulative exposure to silica and not radon [75]. Furthermore, a study of the Colorado Plateau uranium miners showed a particularly high standard mortality ratio from IPF in American Indian compared to white miners (2.79 and 1.94 respectively) [76]. In a study of twenty-two deceased and living uranium miners with evidence of diffuse IPF on a chest radiograph exhibited a UIP pattern of fibrosis with honeycombing in each of the five reviewed lung tissue pathology slides (autopsies or wedge biopsies). Additionally, four out of the five cases exhibited anthracosilicotic nodules [77]. Given the multiple exposures in uranium miners, the exact etiology of this fibrotic pattern is unclear but is believed to be mainly due to radon exposure rather than uranium.

Vanadium

Vanadium is a naturally occurring metal that is extracted by mining or recycling furnace ash from power plants fueled with oils containing vanadium and from spent catalysts [78]. As a transition metal, vanadium exists in several oxidation states, the most common being vanadium pentoxide (V_2O_5) [79]. Occupationally, V_2O_5 exposure occurs primarily via inhalation during oil and coal combustion and from metallurgical works common in the petrochemical, mining, and steel industries [79]. In addition to occupational exposures, ambient exposure to high levels of vanadium can occur as a result of accidental or intentional burning of fuel oils, such as the reported exposures during the Kuwait oil fires in 1991 [80]. Not surprisingly, vanadium is an elemental component of ambient air particulate matter (PM), varying in concentration regionally, but frequently elevated near sources that use residual oil or coal for combustion [81]. Inhalational exposure to vanadium-containing PM has long been associated with adverse respiratory and cardiovascular health effects [82]. In humans, inhalational exposure to vanadium-containing PM is associated with pulmonary function impairment and symptoms suggestive of airway diseases such as bronchitis, airway hyper-reactivity and asthma [83–87]. In one case report, acute decline in FEV1 and FVC were associated with recent exposures to vanadium-rich PM, with peripheral and BAL neutrophilia, indicative of neutrophilic alveolitis [88]. In a large multicenter cohort study, reduced FVC was associated with the vanadium content of ambient PM [89]. Although it is

postulated that chronic vanadium exposure can cause pneumonitis [90–92], there are no human studies supporting a direct link between inhalational exposure and interstitial or diffuse parenchymal lung diseases, particularly IPF. Animal and *in vitro* studies, however suggest that inhalational vanadium exposure may play a role in IPF.

In an animal study investigating the effect of inhalation exposure to V_2O_5 (0.5 mg/m^3), significant increases in chronic inflammation, interstitial fibrosis and alveolar and bronchiolar hyperplasia/metaplasia were observed in both male and female rats [93]. Collagen deposition in subepithelial fibrotic lesions in the peribronchiolar region was present at day 15 after V_2O_5 instillation. In an additional animal study, exposure of human lung fibroblasts to V_2O_5 resulted in a change of over 1400 genes according to an Affymetrix gene array [94]. Induction of genes that mediate cell proliferation and chemotaxis (*VEGF*, *CTGF*, *HBEGF*) in addition to suppression of growth arrest and apoptosis genes were directly involved in the lung fibrotic reaction to V_2O_5 . These data suggest that several genes are involved in airway remodeling after exposure to V_2O_5 . When assessing genetic susceptibility to IPF in mice induced by vanadium pentoxide (V_2O_5), pulmonary responses to V_2O_5 were significantly greater in DBA/2J mice compared to C57BL/6J mice [95]. There were significant dose-dependent increases in lung permeability, inflammation, collagen content and dysfunction. Fibrotic responses in DBA/2J mice persisted 4 months following exposure, while fibrosis in C57BL/6J mice had resolved. A recent study comparing particulate toxicity from samples obtained near an abandoned, unremediated carnotite (uranium/vanadium) mine found that PM derived from mine site sediments, which evidently contained higher levels of vanadium and uranium, exhibited greater *in vivo* and *in vitro* toxicity compared to background dusts [96]. While these studies were all acute pulmonary response assessments, it was further established that vanadium, alone, can drive much of the toxicity and inflammatory outcomes. Such studies are being further pursued to identify whether such sources, numerous in the southwestern US [97], are a possible driver of elevated fibrosis and silicosis observed in the four-corners region [6].

Susceptible/vulnerable populations

Recent geographic hotspots of pulmonary fibrosis mortality in regions inhabited largely by American Indians [6], highlights potential concerns related to environmental health disparities. Although the terms are often used interchangeably, susceptibility is not the same as vulnerability. Susceptibility implies a greater risk for a health outcome at any particular level of exposure, primarily due to biological or intrinsic factors. On the other hand, vulnerability refers to a greater risk for a health outcome due to a greater likelihood of exposure incidence or higher exposure levels. Key factors for predisposing susceptibility range from age-related susceptibility seen in the very young or the elderly, to susceptibility observed with relation to several factors including gender, pregnancy, lifestyle, obesity, race/ethnicity, socioeconomic status, pre-existing diseases, psychosocial adversity, genetics, and epigenetics. For vulnerability, socioeconomic status is a key factor along with other measures of adversity such as race/ethnicity, sex, rural residence, and residential neighborhood segregation. Thus, many overlapping factors may affect both susceptibility and vulnerability to environmental and occupational exposures. The issue of vulnerability fits under the general concept of health equity and environmental justice. While

susceptibility across the population needs consideration when setting concentration limits for exposure, vulnerability needs to be considered in developing control strategies [98]. Hence, it is a public health imperative to understand the factors that alter host susceptibility and vulnerability to metal exposure. An example of a population that is both susceptible and vulnerable to adverse effects of uranium exposure is American Indian workers. The susceptibility of this population is reflected in studies that demonstrate greater odds for radiographically defined lower lobe predominant fibrotic pneumoconiosis compared to non-Hispanic whites, as previously described [74, 73]. Additionally, lung function impairment in American Indian uranium workers, whether obstructive or restrictive appears to be directly related to underground mining rather than other risk factors such as smoking, indicating vulnerability [74]. Furthermore, lung function decline over time appears to be more rapid in American Indian uranium miners despite their lower overall tobacco use, indicating susceptibility [74]. Both susceptibility and vulnerability may help explain the particularly high standard mortality ratio from IPF among American Indian uranium miners compared to their white counterparts [76].

Conclusions

Several important themes emerge during this review. The incidence of idiopathic pulmonary fibrosis is increasing worldwide [4]. A growing body of evidence suggests that the reason for this increase may partly lie in occupational and environmental exposures (Table 1). The American Thoracic Society carefully excludes occupational and environmental lung diseases from the diagnosis of idiopathic pulmonary fibrosis [99]. Therefore, the most important step towards uncovering a possible occupational or environmental cause for an illness in the individual patient is a careful and complete history taking by the treating provider. In the absence of careful consideration of the occupational and environmental history, secondary IPF may be mistaken for idiopathic pulmonary fibrosis, with important implications for both disease management and prognosis. Concomitant occurrence of obstructive and other interstitial lung disease phenotypes in exposed subjects adds to the heterogeneity of the phenotype of secondary IPF. Another theme that emerges is that while most secondary IPF arise from occupational exposures in workers, some may result from environmental exposures in the general population such as arsenic. Confirmation of exposure to metals may require additional analysis of metal concentration in the blood or urine, elemental analysis on bronchoalveolar lavage, biopsy tissue, or autopsy material as well as additional analytic techniques. A UIP pattern on an HRCT scan is highly predictive for the presence of UIP pattern on surgical lung biopsy [2]. There is however a paucity of studies using HRCT, which constitutes a major limitation in this area of research. Moreover, since workers who are occupationally exposed to specific metals may also be exposed to additional metals and nonmetals as well as cigarette smoking, mixed exposures often obscure possible occupational or environmental origin of IPF in an individual patient. The efficacy of specific chelation therapy for patients suffering from metals-induced chronic fibrotic lung disease needs to be substantiated [100, 101]. The role of corticosteroids/anti-inflammatory medications and the recently discovered antifibrotic agents is not established. Supportive treatment could however help in reducing many symptoms of affected patients.

Another major theme that emerges in reviewing recent developments in metal-related lung toxicity is the extent to which various metals are capable of inducing both antigen-specific immune reactions in the lung and nonspecific “innate” immune system responses characterized by inflammation frequently triggered by oxidative damage. With the recognition of these immune and inflammatory effects comes a growing awareness of the potential hazards to the lung at low levels of exposure. Overall, major research gaps were noted for mechanistic studies to identify fibrogenic pathologies in preclinical models. Most animal studies are not appropriately designed to address such an outcome. Studies are typically too short in duration and lack the histological and pathophysiologic rigor to adequately characterize a fibrotic outcome. Moreover, the limited number of fibrotic lung disease models creates challenges for linking to very specific clinical definitions for human pathologies [102]. Much work will be needed to better mechanistically understand pulmonary fibrosis as a consequence of inhaled metal-based dust associated with environmental and occupational exposures.

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A Age-standardized mortality rate from interstitial lung disease and pulmonary sarcoidosis, both sexes, 2014

Figure 1:

A. Age-standardized mortality rate for interstitial lung disease and pulmonary sarcoidosis in 2014. [Used with permission from the Copyright Clearance Center, JAMA, Dwyer-Lindgren et al., 2017.] B. Summary of preclinical and clinical findings of metals-induced interstitial pulmonary fibrosis.

Table 1.

Summary of reported clinical, histopathological, and mechanistic evidence of metals-induced pulmonary fibrosis

Metal	Exposure type	Clinical evidence	Histopathological evidence	Mechanistic evidence
Aluminum	Occupational	Workers exhibit UIP and aluminosis and other interstitial lung diseases	Increase in BAL cells	Elevated MMPs, neutrophil influx, collagen deposition, and proinflammatory cytokine increase
Arsenic	Environmental	Abnormal lung biopsy with pulmonary fibrosis in exposed children; chronic lung disease, skin lesions, lower FVC and FEV, altered lung function; COPD, Bronchiectasis seen on chest X-ray and HRCT scans	Elevated lung dry weight, and collagen deposition in the lungs	DNA oxidation elevated, total glutathione levels decreased
Cadmium	Occupational Environmental	Workers exhibited interstitial fibrosis, low FVC	Septum wall thickening, alveolar lung inflammation	DNA damage, increased inflammatory markers (IL-1 β , TNF- α), MMP-2 and -9, and LDH activity
Copper	Occupational			Upregulation of fibrosis marker, α -SMA, epithelial apoptosis, ROS, significantly upregulated BAL cytokines
Molybdenum	Occupational	Exposed and symptomatic workers exhibit subacute alveolitis; Mixed-metal exposure causes reduced lung function and pneumoconiosis		
Tungsten and Cobalt	Occupational	Workers exhibit UIP, NSIP and other interstitial lung disease patterns, under the umbrella term hard metal lung disease	Particulates invading focal areas of alveolar space	LDH release, superoxide anion production
Uranium	Occupational	Upper lobe chest radiograph consistent with silicosis; abnormal lower lobe chest radiograph consistent with UIP; obstructive and restricted lung function observed	Neoplasia, fibrosis, lung biopsy with UIP pattern of fibrosis	TNF- α secretion, MAPK activation
Vanadium	Occupational	Decline in FEV1 and FVC	Collagen deposition, airway smooth muscle cell thickening, mucous cell metaplasia, fibrosis, alveolar hyperplasia	Upregulation of genes mediating cell proliferation (VEGF, CTGF, HBEGF)