Heavy Metals

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Introduction

There is no consensus on what is or is not a "heavy" metal and our selection (Table 1) is based on a set of criteria relating to density, atomic weight and atomic numbers which we think most authorities would recognize. Some of the listed elements and their compounds are not known to have respiratory toxicity and are not discussed further. Among the remainder it is rarely the metal itself which is toxic; rather, problems arise from inhalation of one or more of its compounds or salts. We will not address the issue of "extraction" of the metals but note that in mining them there are often risks arising from exposures to respirable silica or radon, and that in refining them there may be risks from contaminating exposures; for example, in copper smelting there is frequently co-exposure to arsenic fume, a well-known lung carcinogen.

Table 1 Heavy metals covered in this article with their associated respiratory hazards.

Heavy metals with known respiratory hazards	
Antimony (Sb)	Metal fume fever, pneumoconiosis
Arsenic (As)	Lung cancer
Cadmium (Cd)	Pneumonitis, emphysema, lung cancer (?)
Chromium (Cr)	Lung and sino-nasal cancer, perforation of nasal septum
Cobalt (Co)	Hard metal disease, occupational asthma
Copper (Cu)	Metal fume fever, hypersensitivity pneumonitis
Indium (In)	Pneumoconiosis, alveolar proteinosis
Iridium (Ir)	Occupational asthma
Iron (Fe)	Pneumoconiosis ("siderosis"), pneumonia, metal fume fever
Manganese (Mn)	Metal fume fever, pneumonia
Mercury (Hg)	Toxic pneumonitis
Molybdenum (Mo)	Pneumoconiosis, alveolitis
Nickel (Ni)	Lung and sino-nasal cancer, metal fume fever, occupational asthma
Palladium (Pa)	Occupational asthma
Platinum (Pt)	Occupational asthma
Rhodium (Rh)	Occupational asthma
Silver (Ag)	Argyrosis, metal fume fever
Tin (Sn)	Pneumoconiosis ("stannosis"), metal fume fever
Zinc (Zn)	Metal fume fever, pneumonitis
Heavy metals with no known respiratory hazards	
Bismuth (Bi)	–
Gold (Au)	–
Lead (Pb)[a]	–
Polonium (Po)[a]	–
Thallium (Tl)	–

[a]Radioactive isotopes of lead and polonium (^{210}Pb and ^{210}Po) were discovered in tobacco in 1964 and may contribute to the carcinogenic effects of smoking cigarettes (Moeller and Sun, 2010; Karagueuzian et al., 2012).

Box 1 Heavy metals as respiratory carcinogens.

Several of the heavy metals are known carcinogens. The table below lists the current classifications—in relation to respiratory cancers - determined by the International Agency for Research in Cancer (IARC). For updates, see: https://monographs.iarc.fr/list-of-classifications-volumes/

Metal (compounds)	*IARC classification (group[a])*
Antimony trisulphide	3
Antimony trioxide	**2B**
Arsenic compounds	1
Cadmium and cadmium compounds	1
Chromium metal	3
Chromium(III)	**3**
Chromium(VI)	**1**
Cobalt compounds with tungsten carbide	2A
Cobalt and cobalt compounds without tungsten carbide	**2B**
Indium tin oxide	2B
Iridium	Not classified
Manganese	Not classified
Molybdenum trioxide	2B
Nickel compounds	1
Nickel metal and alloys	**2B**
Palladium	Not classified
Platinum	Not classified
Rhodium	Not classified
Silver	Not classified
Tin	Not classified
Zinc	Not classified
Processes	
Iron and steel foundry work	1
Welding (fume)	1

[a]Group 1: There is sufficient evidence of carcinogenicity in humans. The agent is carcinogenic to humans. Group 2A: There is limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals. The agent is probably carcinogenic to humans; Group 2B: There is limited evidence of carcinogenicity in humans and less than sufficient evidence in experimental animals. The agent is possibly carcinogenic to humans; Group 3: The evidence is inadequate in humans and inadequate or limited in experimental animals. The agent is not classifiable as to its carcinogenicity to humans.

Below, each metal is covered separately, in alphabetic order, with a description of its production and uses, its respiratory hazards and, where appropriate, a brief comment on biological exposure monitoring. In some cases, the diseases caused by these metals are clinically discrete and readily attributable if an accurate exposure history has been acquired; the various pneumoconioses and metal fume fevers are examples of such. In others, notably the lung carcinogens (see Box 1), the disease is clinically indistinguishable from that caused by other agents such as cigarette smoke and attribution of cause and effect is seldom possible at an individual level, with any certainty. The respiratory risks of exposures to heavy metals are largely, but not entirely, confined to those with occupational exposure(s). The risks to the general population are lower but will depend on the effectiveness of controls on industrial emissions to the atmosphere; in some parts of the world these remain rudimentary at best.

Many of the metals discussed below have adverse effects far beyond the lung, and all are significant environmental toxins. For these reasons, their use in many parts of the world has, with some exceptions (such as iron and nickel), been curtailed in recent decades. At the same time, some such as indium have found new uses in developing technologies and, consequently, new types of respiratory toxicity have emerged.

Individual Heavy Metals

Antimony

Production and sources of exposure

Antimony is a metalloid which occurs mainly as the sulphide mineral stibnite (antimony trisulphide Sb_2S_3) in metamorphic deposits in granites and limestone. Worldwide, the greatest producer of antimony is China followed by Russia and Bolivia. Antimony metal and various antimony compounds (such as antimony trioxide and trisulphate) are produced from the ore. Exposure to antimony dust occurs during the mining, crushing and processing of the ore; however the highest exposures to both antimony dust and fumes are likely to occur in smelting and refining processes.

Antimony is most commonly used as antimony trioxide in the manufacture of flame-retardant materials. It has also been used as an alloy with lead in the production of microelectronics, solders, lead-acid batteries, bullets and bearings, and in pewter (an alloy of tin, copper and antimony). Other uses of antimony compounds include(d) as a pigment in paints, textiles and glass industries, in the production of the thermoplastic polymer polyethylene terephthalate (PET or "terylene"), as a semiconductor in the electronics industry, to make the red tips of safety matches and in antiprotozoal veterinary drugs.

Respiratory toxicity

Non-specific respiratory symptoms such as cough, wheeze and upper airways symptoms (rhinitis and septal ulceration) have been reported in antimony-exposed workers. Acute chemical pneumonitis with pulmonary oedema has been described in antinomy smelters from the 1950s (Renes, 1953). Antimony pneumoconiosis is rare and occurs due to inhalation of quartz-free antimony trioxide powder but has no impact on health or life expectancy. Its radiological appearances develop after 10 or more years of exposure; typically, numerous small, dense opacities similar to those in siderosis (varying from ILO category 1p to 3p) are seen in the absence of confluent opacities. The hilar lymph nodes may be radio-dense but are not enlarged (Potkonjak and Pavlovich, 1983). The pathological appearances include antimony particles in dust-laden macrophages in the alveolar wall and in the perivascular regions of the lungs but there is no fibrosis or inflammatory reaction (McCallum, 1967). The biological half-life of antimony in the lungs appears to be greater than 20 years. Antimony miners are usually co-exposed to high concentrations of quartz and thus antimony pneumoconiosis may co-exist with or be confused with silicosis.

Biological monitoring

Antimony may be measured in urine but little is known how levels there relate to exposure (Bailly et al., 1991).

Arsenic

Production and sources of exposure

Like antimony, arsenic is technically a "metalloid." Arsenic-containing minerals are mined chiefly in China but also in Morocco and Russia; arsenic is also found as a contaminant in non-ferrous (copper, lead, and gold) smelting. Its primary use is in alloys of lead (in car batteries and ammunition); gallium arsenide is used in the production of semiconductors. The use of arsenic as a veterinary pesticide and in timber preservation has been largely phased out.

Respiratory toxicity

Arsenic is a lung carcinogen (Box 1) whether through inhalation (in smelting operations), ingestion of contaminated water (Celik et al., 2008) or by direct contact; indeed the first report implicating this role was a study of English workers in a factory producing sheep dip (Hill and Faning, 1948).

Biological monitoring

Arsenic and its metabolites may be reliably measured in urine samples (Morton and Leese, 2011).

Cadmium

Production and sources of exposure

There are no significant deposits of cadmium-containing ores and the metal is obtained as a byproduct of the mining, smelting and refining of zinc, lead or copper ores with which it is geologically associated.

Cadmium was used as a corrosion-resistant plating on steel, and cadmium compounds produce red, orange and yellow pigments to color glass and to stabilize plastic; in the past it was a fairly common component of brazing and soldering alloys. Its environmental toxicity has led to it being phased out of many materials; nickel-cadmium batteries, for example, have been largely replaced by lithium-ion and nickel-metal hydride equivalents. One of the few novel uses of cadmium is in the manufacture of thin-film, cadmium telluride solar panels. A significant route of exposure to cadmium fume is through the smelting and refining of non-ferrous metals (notably zinc, lead, and copper) and in the recycling of cadmium-containing materials.

Respiratory toxicity

High exposures to cadmium fume can induce an acute, toxic pneumonitis, which may be lethal (Patwardhan and Finckh, 1976); because cadmium oxide is insoluble, its adverse effects may have a latency of several hours. Lower, more chronic exposures give rise to pan- and centri-acinar emphysema. The strongest evidence for this derives from a cohort study of men who worked in a copper-cadmium alloy plant in the United Kingdom, in whom deficits in transfer factor increased linearly with estimates of cumulative exposure to cadmium fume (Davison et al., 1988). The mechanism for this effect is unknown but cadmium contamination of tobacco may explain some of the deleterious effects of cigarette smoking (Ganguly et al., 2018).

Cadmium and its compounds are an established lung carcinogen (Box 1) although the evidence base is weaker than for some of the other heavy metals.

Biological monitoring

The main target organ of cadmium toxicity is the kidney; urinary levels increase with age and reflect total body burden. In contrast, levels in blood are an indicator of recent exposure only. The half-life of the metal may be as long as 30 years; it accumulates not only in the kidneys but also in the liver, and in both organs its concentrations may be measured through neutron activation or X-ray fluorescence.

Chromium

Production and sources of exposure

Chromium is mined—as its ore "chromite"—in South Africa, Kazakhstan, India, Russia, and Turkey. Almost 90% of chromium is accounted for in the production of steel alloys (including "stainless" steel) or in electroplating. Other uses include in tanning where trivalent chromium salts such as chrome alum cross-link collagen fibers, so stabilizing the leather. Chromite has high heat resistance and is used in high temperature refractory applications such as blast furnaces and cement kilns. Chromium compounds are used as catalysts in the production of man-made hydrocarbons such as polyethylene; and, together with copper and arsenic, in wood preservatives. Finally, several chromium salts are strong and durable pigments and are used in dyes and paints, including those that once colored German postboxes and school buses in the US bright yellow. Concerns over contamination of water and soil have led to the replacement of chromium compounds in several applications.

Chromium compounds exhibit several oxidation states, the most common of which are chromium(III) and chromium(VI), "trivalent" and "hexavalent" chromium respectively. Chromium(III) compounds are generally stable and water insoluble and are not known to be toxic; similarly chromium metal itself is non-toxic. In contrast, chromium(VI) compounds are oxidants and recognized to be highly toxic.

Respiratory toxicity

For over a century, chromium(VI) compounds have been known to be respiratory tract carcinogens; Langard (1990) provides an interesting review of the early literature in which the first reported case was of nasal cancer in a chrome pigment worker in Scotland. There is now a far more extensive literature relating to lung cancers, comprehensively reviewed by the International Agency for Research into Cancer, which has categorized hexavalent chromium compounds as a Group 1 carcinogen (see Box 1). A systematic review of occupational cohort studies estimates, on the basis of absolute excess risks, that exposures to chromium(VI) at a level above 1 mg m^{-3} induce more than 4 lung cancers per 1000 exposed workers (Seidler et al., 2013).

Chromium salts are also potential sensitisers and an uncommon cause of occupational asthma (Walters et al., 2012); far more commonly they cause a contact dermatitis and, notoriously, "chrome ulcers" of the skin and perforation of the nasal septum.

Biological monitoring

Chromium(VI) is converted in the body to chromium(III) and excreted in urine. In those exposed to chromium compounds at work, urinary levels rise across a working shift and reflect also high cumulative exposures after which levels may not return to normal for several years. Chromium may also be measured in blood but this is a less reliable measure of accumulated exposure.

Cobalt

Production and sources of exposure

Cobalt is a silvery blue-white metal with magnetic properties. Most cobalt is obtained as a by-product of nickel and copper mining and smelting; the largest global producer currently is the Democratic Republic of Congo. Various grades of cobalt powder are manufactured; extra-fine cobalt is used in the manufacture of 'hard' metal (a composite of tungsten carbide, carbon black and cobalt) which has exceptional properties of resistance to heat and wear and is thus used for high-speed cutting tools. Cobalt has a wide range of other uses which include production of high-performance alloys such as those used in electronics, high strength steels and in prosthetic joints. It is also used in rechargeable batteries, as a blue pigment in glass and paint and as a catalyst in the chemical and oil industries.

Respiratory toxicity

Cobalt is a known respiratory sensitiser and a cause of occupational asthma after exposure to cobalt dust alone (e.g., during milling of cobalt metal) with specific inhalation challenge testing demonstrating early, dual and late responses (Walters et al., 2012). It is also a cause of interstitial lung disease (ILD) in the hard metal and diamond-bonded tool (where cobalt powder is used as a matrix for diamonds) industries. This ILD is referred to by various names including Cobalt Lung, Giant Cell Interstitial Pneumonitis (GIP) and hard metal pneumoconiosis. The underlying mechanism responsible for cobalt related ILD is thought to be an immune-mediated process or oxidant injury.

In the subacute form of cobalt related ILD, symptoms occur at the time of exposure often improving away from exposure and include dyspnoea, cough, and constitutional symptoms of fevers, chills, and weight loss; the latent period is months to a few years after exposure. Complete resolution may occur if exposures cease. In the chronic form, as with other fibrotic lung disease, it presents with insidious onset of dyspnoea and cough, without a clear work-related pattern and constitutional symptoms do not occur.

Radiological changes are non-specific and variable and may resemble those of non-specific or usual interstitial pneumonitis, sarcoidosis or hypersensitivity pneumonitis. The pathology is of a Giant Cell Interstitial Pneumonia; the presence of "cannabilistic" multinucleated giant cells in bronchoalveolar lavage is diagnostic in the context of an appropriate occupational history and radiological changes, otherwise lung biopsy is required. Removal from exposure is the most important management option although is less likely to result in remission in those with chronic disease or established fibrosis (Adams et al., 2017).

There are reports of acute pulmonary oedema after exposure to high concentrations of cobalt fume e.g., during melting and pouring of metal into molds. As an aside, cobalt may also cause a cardiomyopathy.

Biological monitoring

Urinary cobalt can be measured, usually at the end of a shift and correlates well with levels of exposure. The half-life is approximately 2–3 days and so levels may accumulate during the working week.

Copper

Production and sources of exposure

Copper ores are mined widely, most notably in Chile, Peru, China and the United States but also in parts of central Africa and in Mexico and Indonesia; unusually the metal is also found in its pure form, which in part accounts for the antiquity of its use. Copper has high thermal and electrical conductivities and is very widely used in electric cabling, in electrical motors and in printed circuit boards. Its resistance to corrosion allows it to be used in plumbing, roofing and cladding and, in the past, as a covering for ships' hulls. In alloy with other metals such as nickel, it is used in coinage and in the making of jewelry. Despite being an essential trace element for animals and plants, copper is toxic to many micro-organisms and is used increasingly in antimicrobial systems including, as a copper sulphate solution neutralized by hydrated lime ("Bordeaux mixture"), a fungicide to control mildew on grape vines. Copper is widely re-cycled and it is estimated that 80% of the extracted metal is still in use.

Respiratory toxicity

Copper fume is a rare cause of "metal fume fever" (see Box 2). Bordeaux mixture is a recognized cause of hypersensitivity pneumonitis in vineyard workers who are exposed during spraying; suggestions that it is also a lung carcinogen have not been widely confirmed (Santic et al., 2005). The inhalation of fine copper "dust" has been reported to cause mild 'flu-like symptoms (Gleason, 1968).

Box 2 Metal fume fever (MFF)—See also "zinc".

MFF is a clinical syndrome arising from the inhalation of metal-containing fume, usually during welding or related processes. It is a self-limiting condition characterized by fever, myalgia, headache, cough and a leucocytosis; typically, physical examination and chest radiography are normal. MFF is tachyphylactic, being worst after an exposure-free period such as a weekend and lessening over the course of the working week, a pattern reflected in one of its several vernacular names ("Monday fever").

Proinflammatory cytokine release is probably important in the pathogenesis of MFF. Bronchoalveolar lavage fluid analysis following experimental zinc oxide welding fume exposure in human subjects (Blanc, 1993) demonstrated significant time- and dose-related increases in the concentrations of tumor necrosis factor (TNF), IL-6 and IL-8 with the highest concentration of TNF at 3 h post exposure compared with 8, 20 or 22 h post exposure, mimicking the time course of MFF.

By far the commonest cause of MFF is zinc oxide fume but oxides of other metals, several of them "heavy," have been implicated:

- Aluminium
- Antimony
- Beryllium
- Boron
- Cadmium
- Chromium
- Cobalt
- Copper
- Iron
- Manganese
- Magnesium
- Nickel
- Silver
- Selenium
- Tin
- Vanadium
- Zinc

For a full review of the history, epidemiology and toxicology of MFF see Greenberg and Vearrier (2015).

Indium

Production and sources of exposure

Indium is a rare, post-transition metal produced largely as a by-product of the processing of other metal ores. The global demand for indium has increased rapidly due to the use of indium-tin oxide (ITO), a sintered alloy (comprising 90% indium oxide and 10% tin oxide), in the manufacture of transparent conductive coatings for liquid crystal displays, touchscreens and solar cells. Exposures to indium metal and indium compounds can occur during ITO production, in the manufacture of ITO containing coatings and in the recycling of these products. The majority ITO is used in South East Asia, primarily Japan, China, Taiwan, and South Korea.

Respiratory toxicity

ITO is a recognized cause of lung disease in humans (Homma et al., 2003) with a strong relationship between exposure, respiratory symptoms and abnormal physiology (Cummings et al., 2016). Cases of both interstitial lung disease (ILD; with median latency of 3 years) and pulmonary alveolar proteinosis (PAP; with a latency of just 6–14 months) have been reported. The ILD is associated with normal or obstructive spirometry, preserved or modestly reduced diffusing capacity, radiological appearances of fibrosis and emphysema, lymphocytosis or increased macrophage count on bronchoalveolar lavage and prominent fibrosis on histopathology. The reported cases of PAP had typical physiological changes with restrictive spirometry and reduced diffusing capacity and classical "crazy paving" on CT scan. Clearance of ITO from the lungs is slow with disease progression (in both ILD and PAP cases) even after removal (Cummings et al., 2012).

In both ILD and PAP cases, indium was identified on lung biopsy with particles visible under light microscopy. Common pulmonary histopathologic features in these patients included intra-alveolar exudate typical of alveolar proteinosis, cholesterol clefts, granulomas and fibrosis.

Iridium (See Also Platinum)

Production and sources of exposure

Iridium, a platinum group metal, is the most corrosion-resistant metal known. It is found as an element in natural alloys (especially in combination with osmium) and as compounds in nickel and copper deposits. The main use of iridium is in electronics applications, spark plug manufacture, electrodes for the chloro-alkali process (in the electrolysis of sodium chloride) and in chemical catalysts.

Respiratory toxicity (see also platinum)

In its elemental form iridium powder may be a respiratory irritant; while there are no reports of occupational asthma due to iridium salts it is likely that some are hazardous in that respect.

Iron

Production and sources of exposure

Iron is a transition metal which occurs naturally as iron ores from which metallic iron is extracted and is the most commonly used heavy metal. Important ores include magnetite (iron (II, III) oxide—Fe_3O_4), hematite (iron (III) oxide—Fe_2O_3), limonite (a mixture of hydrated iron (III) oxide-hydroxide in varying compositions (FeO(OH)) and goethite (FeO(OH))). Pig iron or crude iron is an intermediate product of the iron industry made by smelting iron ore into an ingot of impure high-carbon iron which contains silica and other impurities.

Iron ore mining is carried out across the globe and particularly so in China, Brazil, and Australia. The vast majority of mined iron ore is used in steel manufacture; other important uses include welding and as a pigment in paints. Exposure to iron and iron oxide fumes occurs in producing steel and cast iron, iron mining, crushing of iron ore and the welding, grinding and finishing of iron products. Of note, whilst exposure to iron is common, the reporting of pneumoconiosis related to iron (siderosis) is rare.

Respiratory toxicity

High exposure to iron can cause siderosis which is a radiological diagnosis and is not associated with any clinical symptoms or lung function deficit unless there has been concomitant exposure to other elements (such as quartz) which can then give rise to a "mixed dust" fibrosis. The chest radiograph appearances of siderosis include small, uniform radio-dense opacities and the absence of large conglomerates. The shortest reported latency is 3 years after high exposures, but most changes occur after many years (Kleinfeld et al., 1969). Occasionally, in advanced disease, fine dense linear opacities are apparent in the lung parenchyma with the presence of Kerley b lines; lymph nodes may be radiodense but are not enlarged. Radiological improvement may be seen with cessation of exposure as iron dust is slowly eliminated from the lungs.

An increased excess risk of mortality from pneumonia in welders has been observed since the middle of the 20th century. Closer analyses demonstrated that the deaths were primarily from lobar pneumonia (rather than bronchopneumonia) and were highest in those working with ferrous metal fume (Palmer et al., 2003). Possible hypotheses that may explain this observation include inhaled iron acting as a growth nutrient for microorganisms, or that the metal fume causes oxidative damage to host lung defenses, thus impairing immune responses (Coggon and Palmer, 2016). Welders may benefit from pneumococcal vaccination; importantly, the risk appears to diminish after cessation of exposure.

Manganese

Production and sources of exposure

Manganese ores, chiefly pyrolusite (MnO_2), are mined mainly in South Africa but there are smaller deposits in Australia, China, Brazil, India, Ukraine and some African and Asian states. Almost all manganese is used, for its anti-corrosion properties, in iron or aluminium alloys. Other uses include as a cathode in some batteries and as a pigment.

Respiratory toxicity

Inhalation of manganese fume is a rare cause of metal fume fever (Box 2). As is the case with some other metal fumes, manganese exposure may increase the risk of pneumonia, a subject well covered by Bergstrom (1977).

Biological monitoring

Manganese levels may be assayed in blood and urine although the value of these is debated; urinary manganese levels seem mainly to reflect current exposure (only around 1% of absorbed manganese is excreted in the urine) while blood manganese concentrations may be a better indicator of body burden (Lucchini et al., 1995).

Mercury

Production and sources of exposure

Mercury is mined largely through its ore, cinnabar, although the metal is occasionally found in its pure state. The largest mines now are in China and Kyrgyzstan. Because of its significant toxicities—most of which are non-pulmonary—the uses of mercury are far fewer than they were but the metal is still used in some sophisticated electrical and electronic applications such as high-temperature thermometers, in some fluorescent lamps and in dental amalgams.

Respiratory toxicity

Inhalation of mercury vapor may give rise to a toxic pneumonitis with respiratory symptoms developing a few hours after exposure followed by gastro-intestinal symptoms (nausea, vomiting, abdominal pain) and joint pains. Clinical examination will reveal diffuse, basal crackles; radiological findings in the acute phase are similar to those of pulmonary oedema (Seaton and Bishop, 1978). After high exposures the condition may be fatal; survivors may be left with a diffuse interstitial pneumonia characterized by restrictive defects in lung function and typical radiographic changes. Importantly, significant exposures may occur outside the workplace through recreational use (Gore and Harding, 1987) or accidents in the home (Gao et al., 2017).

Biological monitoring

Acute poisoning may be detected through a blood mercury level; assay of a spot urine sample reflects cumulative exposure to mercury.

Molybdenum

Production and sources of exposure

Molybdenum is mined as an ore (molybdenite) in China, the United States, Chile, Peru and Mexico. Its chief use is in the production of high-strength steel and other alloys.

Respiratory toxicity

Metal plant workers exposed to molybdenum fume may report non-specific respiratory symptoms at work but appear to have no associated deficits in lung function or radiographic changes; a report of lymphocytosis on bronchoalveolar lavage may indicate a (sub-)clinical alveolitis (Ott et al., 2004).

Pneumoconiosis has been reported in dental technicians working with cobalt-chromium-molybdenum alloys (Selden et al., 1996).

Nickel

Production and sources of exposure

Nickel is a silvery transition metal which is cheap and widely available. It is often found in combination with iron in limonite or as an oxide or sulphide ore and is extracted from these ores by roasting and reduction. Exposure to insoluble nickel occurs in mining, refining and smelting; exposure to soluble nickel takes place in a wide range of industries including those making alloy and stainless steel, electroplating, batteries, paint textiles and in chemical manufacture. The vast majority of nickel is used in manufacture of stainless and alloy steels and in nonferrous alloys. Nickel salts are used in electroplating, ceramics and pigments and as catalysts.

Respiratory toxicity

Nickel, probably most commonly known for causing contact dermatitis, may also cause occupational asthma. Exposure to nickel oxide fumes is a rare cause of metal fume fever (see Box 2). Nickel carbonyl, $Ni(CO)_4$, is a heavy colorless unstable liquid which

vaporizes at 43 °C; the vapor is highly toxic and inhalation may cause acute symptoms of nausea, vomiting, headache and upper airway irritation with resolution, followed by the development over the next 36 h (or occasionally longer) of chemical pneumonitis and pulmonary oedema which may be fatal. There is no specific treatment and management is supportive (Shi, 1986).

Chronic exposure to nickel may cause rhinitis, sinusitis, asthma, chronic bronchitis, emphysema and nasal septal perforation in individuals working with nickel or nickel compounds.

The association between nickel work and cancer was first made in the 1930s at the Mond Nickel Works in South Wales. Subsequently, a large body of evidence has accumulated to indicate an increased risk of lung, nasal and sinus cancer among nickel refinery workers and an elevation in lung cancer risk among nickel smelters with the evidence being strongest for water-soluble nickel compounds and lung cancer (see Box 1).

Biological monitoring

For workers exposed to soluble nickel compounds urinary nickel can be measured, usually at the end of a shift, and correlates with exposure; levels increase over the working day with a wash-out half-life of 17–39 h and so may accumulate during the working week. The concentration of urinary nickel in those exposed to insoluble nickel compounds reflects the combined influence of long-term accumulation and recent exposures.

Palladium (See Also Platinum)

Production and sources of exposure

Of all the platinum group metals, palladium has the lowest melting point. Its most common use is in catalytic converters but it is also used in electronics, to make some alloys of dental amalgam, health care (blood sugar tests strips and surgical instruments) and in hydrogen purification, chemical applications, groundwater treatment, and jewelry. Palladium is a key component of fuel cells, which react hydrogen with oxygen to produce electricity, heat and water.

Respiratory toxicity (see also platinum)

Palladium salts are a recognized cause of occupational asthma in refinery workers (Daenen et al., 1999).

Platinum and the Platinum Group Metals (PGMs)

Production and sources of exposure

The platinum group metals (PGM) comprise six precious transition metals—ruthenium, rhodium, palladium, osmium, iridium and platinum—which are each rare and highly valuable. They all have similar physical and chemical properties being highly unreactive silvery-white metals. PGMs tend to occur together in the same mineral deposits; the largest reserves are in the Bushveld igneous complex in South Africa followed by those in the Russian Urals and in the Sudbury Basin in Canada. They are most commonly used in catalytic converters for vehicular emission control devices whereby harmful unburned hydrocarbons, carbon monoxide and nitrogen oxide exhaust emissions undergo complete combustion forming less harmful gases—nitrogen, carbon dioxide and water vapor; the recycling of scrapped catalytic converters is another important source.

Platinum is also used to make fine jewelry, in chemical production and petroleum refining, to make electronic contacts and electrodes and laboratory, glass-making and dentistry equipment. It is a constituent of some chemotherapy agents (cisplatin, carboplatin) and is used in the manufacture of the silicone rubber and gel components of medical implants (such as breast implants and joint replacement prosthetics).

Respiratory toxicity

In their elemental form the PGMs are harmless but their (halide) salts are all potential causes of occupational rhinitis and asthma with the greatest risk being to individuals working in precious metal refineries. Most experience is with platinum salts which are potent respiratory sensitisers and appear to act as haptens conjoined to body proteins; skin prick testing is indicative of specific sensitisation which, with ongoing exposure, is highly predictive of subsequent occupational asthma (Merget et al., 2017).

Biological monitoring

Workers in precious metal refineries undergo regular surveillance with skin prick tests to platinum salt solutions.

Rhodium (See Also Platinum)

Production and sources of exposure

Rhodium is found in platinum or nickel ores together with other platinum group metals. The majority of rhodium is used in catalytic convertors but it also has applications in the chemical industry as a catalyst and in jewelry and as a tarnish-resistant coating to sterling silver. Rhodium may be used in an alloy to harden and improve the corrosion resistance of platinum or palladium.

Respiratory toxicity (see also platinum)

Rhodium salts are a rare cause of occupational asthma in refinery workers (Merget et al., 2010).

Silver

Production and sources of exposure

While silver can be found in its elemental, "native form," most is produced as a by-product of copper, gold, lead and zinc processing. Beyond its use in ornamental settings and in some currencies, silver is used as a chemical catalyst, as an electrical conductor, as a backing for mirrors and in "wet" photography. Silver nitrate is antimicrobial and used to impregnate some surgical dressings.

Respiratory toxicity

Silver, and silver compounds, have very low respiratory toxicity. Silver fume is reported to be a rare cause of metal fume fever (Box 2); argyro-siderosis has been described in silver polishers (Barrie and Harding, 1947), but it is unclear whether the inhaled silver has any pathogenic role beyond staining the lung's alveolar walls and small blood vessels.

Tin

Production and sources of exposure

Tin is a silvery white post-transition metal obtained primarily from the mineral cassiterite (which contains stannic oxide SnO_2) by smelting but also in small quantities from tin sulphides such as stannite. Casserite is almost always associated with granite rocks containing substantial amounts of quartz and sometimes radon. Worldwide the largest tin mines are in China, Indonesia or South America. Recycling is important and whilst the US has not mined tin since the 1990s it is the second largest producer of tin from recycling. The proportion of tin in the ore is low and thus mining, crushing and screening are unlikely to cause stannosis but may result in high exposures to respirable crystalline silica. In contrast, concentrates of cassiterite provided to smelters are largely free of quartz and the risks of silicosis are much lower.

Tin is used in many alloys, the first use being in manufacture of bronze (from tin and copper) around 3000 BC; another alloy, pewter contains 85–90% tin with the remainder consisting of copper, antimony and lead. The most common use now of tin is in solder (typically a minimum of 60% tin in combination with lead) but other important uses are in corrosion resistant tinplating of steel for food preservation and in the manufacture of indium tin oxide (ITO). Other uses include in specialized alloy form including niobium (to make superconducting magnets), as a stabilizer in polyvinyl chloride (organtin) and in biocides. Commercial grades of tin (99.8%) also contain small amount of bismuth, antinomy, lead and silver as impurities.

Respiratory toxicity

Inhalation of tin oxide exposure causes stannosis, a benign, non-fibrotic pneumoconiosis. Stannosis is a radiological diagnosis with numerous small very dense opacities scattered evenly throughout the lung fields. The nodules may be larger (2–4 mm) and fluffier or more irregular compared with those of siderosis but confluent opacities do not occur. The hilar lymph nodes are not enlarged but may be radio-dense. The macroscopic appearances of the cut lung show numerous 1–3 mm, gray-black dust macules which are soft to touch and not raised above the lung surface. Microscopic appearances include macrophages laden with tin oxide particles in the alveolar walls and spaces, perivascular lymphatics and interlobular septa, and macules of denser perivascular and peribronchiolar aggregations of dust-laden macrophages. X-ray diffraction can provide definitive identification with the tetragonal crystal of tin oxide being strongly birefringent compared with the poorly birefringent quartz crystals. Stannosis does not cause any respiratory symptoms or abnormal lung function and there is no effect on health or life expectancy (Fig. 1).

Zinc

Production and sources of exposure

Zinc is most commonly found in association with the sulphides of other metals such as copper, iron and lead. One of the most commonly used metals, around 70% of zinc originates from mining and 30% from recycling. It is mined across the globe with the biggest producer being China followed by Peru and Australia. Zinc metal is produced using a process of extractive metallurgy.

Galvanization is the process of applying an anti-corrosion, zinc coating to steel or iron to prevent rusting, and is its most common use. The metal is applied electrochemically or as molten zinc in "hot-dip" galvanizing or spraying. Galvanization is widely used on car bodies, fencing and railings, bridges and metal roofs. The other major use for zinc is in production of brass, bronze and other alloys. Zinc salts are widely used in the manufacture of rubber and plastics, paints and pigments, chemicals and as a preservative.

From a respiratory point of view, most zinc compounds are innocuous but there two important exceptions; zinc oxide, a cause of metal fume fever (see Box 2), and zinc chloride. Zinc oxide fume is generated in a number of different scenarios, the most common being electric arc welding of galvanized mild steel where the combination of high temperatures in an oxygen rich atmosphere causes high concentrations of zinc oxide fume. In contrast, the process of galvanizing at (relatively) lower temperatures does not produce zinc oxide fume. Zinc smelting, arc-air gouging processes and brass foundry work may also generate zinc oxide fume.

Zinc chloride is used in galvanization, in oil refining, in dry batteries and in taxidermy. Zinc oxide in combination with hexachloroethane forms zinc chloride and is used to make smoke bombs for use in military training and in firefighting exercises.

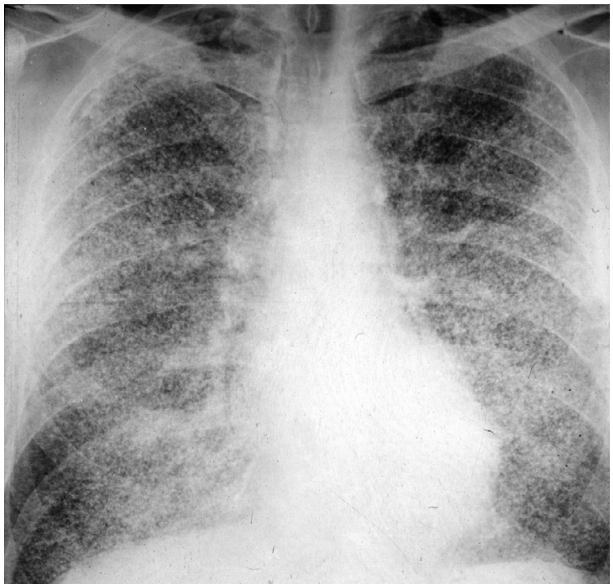

Fig. 1 Stannosis on chest radiography. The particles of tin oxide, being radio-dense, are easily visible as small, rounded opacities throughout the lung fields—but they are biologically inert.

Respiratory toxicity

The inhalation of zinc oxide fume is the commonest cause of metal fume fever (MFF—see Box 2), an inhalation fever known by a variety of eponymous terms depending on the pertinent industry; these include brass founders' ague, galvanisers' fever, welders' shakes or smelters' chills. The clinical features of MFF develop 4–10 h after exposure and typically include non-specific influenza-type symptoms—fevers, rigors, sweating, arthralgia, myalgia, headache and malaise—in addition to a sweet metallic taste, dry cough and breathlessness. Recovery usually occurs after 12–48 h and no specific treatment is required; tachyphylaxis is a feature. While symptomatic, body temperature may increase to 39 °C or more; otherwise physical examination and radiology are usually normal although cases with radiological changes and bronchospasm have been reported (Greenberg and Vearrier, 2015). Laboratory studies may demonstrate leucocytosis with leftward shift or an elevated erythrocyte sedimentation rate. The diagnosis of MFF is clinical, based on an appropriate exposure history, and there is no role for measuring zinc levels in the blood or urine.

A more severe response resulting from high exposures to zinc chloride has been associated with detonation of smoke bombs in military or similar settings. Symptoms develop within 2 h of exposure and initially remit over 6–10 h; but are followed by a severe relapse 24–48 h after exposure with fever, tachycardia and an increasingly productive cough. Radiology may demonstrate diffuse patchy infiltrates and changes mimicking acute respiratory distress syndrome; the condition may be fatal (Blount, 1990).

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