

ALLERGIES IN THE WORKPLACE

Shahidah Adams, MB ChB, MFamMed, DOH
Department of Occupational Medicine, School of Public Health and Family Medicine, University of Cape Town, South Africa.

METALS AND ALLERGY

Introduction

Elements are defined as metals on the basis of their physicochemical properties. From a toxicological perspective metals are defined as elements which under specific biological conditions have the potential to react and lose one or more electrons to form cations. Metals are ubiquitous in our environment and many have been characterised as trace elements or micronutrients essential for the normal biochemical functioning of the human body such as nickel (Ni), vanadium (V), iron (Fe), aluminium (Al) and chromium (Cr). However the potential for toxic effects associated with exposure to metals such as lead (Pb) and mercury (Hg) have been well documented. Many of the earlier studies were initiated after toxic effects were observed affecting subjects in the occupational setting where exposures were high and of long duration.¹ This is particularly true for Pb and Hg exposure. In recent times with advances in immunology, a link between exposure to metals and the development of allergic diseases has also been demonstrated.^{1,2,3} This is of particular relevance in the occupational setting where exposures to sensitising metals commonly occur. Such exposures have not been well studied and are therefore poorly characterised. This poses a dilemma for occupational physicians who need to prevent occupational diseases and for other specialists such as pulmonologists and dermatologists who need to diagnose and treat these disorders.³ This review focuses on the most common occupational allergic disease entities and the role of sensitising metals as aetiological agents.

Mechanisms of sensitisation

Metals implicated in causing sensitisation and allergic disease have been identified as: platinum (Pt); rhodium (Rh); nickel (Ni); chromium (Cr); cobalt (Co), gold (Au); mercury (Hg), zirconium (Zr) and beryllium (Be). For these metals sufficient evidence exists of their sensitising potential.² Sensitising metals are haptens which are not able to act as sensitising agents on their own. In this regard they are similar to other reactive low molecular organic molecules.³ It is postulated that these haptens may combine with circulating or tissue proteins such as albumin, giving rise to new antigens. An alternative hypothesis is that these metals interfere with the antigen-recognition step of the immune response and that immunomodulatory and immunotoxic effects may also play a role in metal-induced hypersensitivity.² Hypersensitivity reactions induced by metals may be classified using the Coombs gel classification system for allergic reactions.

Those metals inducing a type I allergic reaction can be detected by the presence of specific IgE antibodies against metal-human serum albumin conjugates. A type IV reaction in contrast is characterised by a cell-mediated allergic response and has been demonstrated in granulomatous lung disease caused by sensitisation to Be. It is postulated that a cell-mediated allergic reaction may also be involved causing pulmonary fibrosis in subjects exposed to aluminium (Al) and titanium (Ti).³ This same mechanism is responsible for the development of allergic contact dermatitis, with cases commonly occurring as a result of occupational exposure to Ni and Cr (Table I).

Table I. Allergic reactions associated with sensitising metals

Coombs gel reaction	Metals	Disease
Type I	Platinum, rhodium, nickel, chromium, cobalt	Asthma
Type II or type III	Gold salt*	Glomerulonephritis, thrombocytopenia, agranulocytosis
Type III	Mercury	Glomerulonephritis
Type IV	Nickel, chromium, cobalt, rhodium, mercury, tungsten Beryllium	Contact dermatitis Cutaneous granuloma Granulomatous lung disease

*Refers to rheumatoid arthritis patients treated with gold salt therapy and does not denote an occupational exposure.

High-risk occupational exposure settings

Exposures to pure metallic forms of metals or metal-loids are rare. It is more usual for exposure to occur to binary metal compounds such as oxides, sulphides, halides, hydrides and carbides or to multi-element metals such as salts.³ Occupational exposure to sensitising metals is widespread and occurs across many industries. These include metal-processing industries such as alloy production, metal alloy production, smelting, refining and recycling of car components and scrap metal. Industries such as boiler making, steel galvanising and welding involve the assembly of large metal components into finished metallic products. Metals are used in production processes such as electroplating, tanning and cement production while cutting tools containing metal are used in the diamond polishing industry (Table II).¹

Metals may also be contaminants or by-products as in cement manufacture, and exposure to wet cement in the construction industry has been associated with high rates of sensitisation to chromate.⁴

Metals are also used as pigments in the paint industry, as catalysts in the chemical industry and as additives in the plastics industry.³

Correspondence: Dr S Adams, UCT Lang. Institute, George St, Mowbray 7700. Tel. 021-406-6897, e-mail: adams@uctgsh1.uct.ac.za

Table II. Sensitising metal exposure associated with asthma by industry and exposure

Occupation	Exposure
Alloy production	Cobalt
Boilermaking	Chromium, nickel
Cement production	Chromium salts
Diamond polishing	'Hard metal' (5-20% cobalt; may have traces of nickel)
Electroplating	Nickel and chromium salts
Metal alloy production	Cobalt, zinc
Galvanising steel	Zinc
Pigment colouring glass, enamel production	Cobalt
Scrap metal, auto exhaust catalyst recycling, refining	Platinum
Tanning	Chromium
Welding	Chromium, nickel, zinc

(Adapted from Krantz and Dorevitch.¹)

Spectrum of allergic diseases and the epidemiology of allergic sensitisation to metallic allergens

From an occupational perspective, hyperreactivity to sensitising metals manifests predominantly as respiratory or dermatological disease. These manifestations cover a spectrum of diseases with most research focusing on occupational asthma and allergic contact dermatitis. Less frequent manifestations such as extrinsic allergic alveolitis and glomerulonephritis have also been described.¹ A description of the various medical conditions resulting from sensitisation to metals is presented together with the underlying immune reactions implicated in the disease process.

Aluminium (Al)

Occupational Al exposure has been associated with the development of a form of metal pneumoconiosis, viz. aluminium-induced pulmonary fibrosis or 'aluminium-lung'. It is postulated that this entity may present in its early stages as a granulomatous lung disease which is caused by a cell-mediated allergic reaction. One such case report describes a case of sarcoid-like lung granulomatosis in a patient with Al exposure.⁵

Occupational asthma of aluminium smelters (OOAS) also called 'potroom asthma' was first described in 1936 and has been extensively studied since then.⁶ The asthma is not thought to be immune-mediated nor caused by Al, but is ascribed to an inflammatory reaction due to irritation by fluorides.³

Beryllium (Be)

Berylliosis or chronic beryllium disease (CBD) is well known for its striking histological and clinical resemblance to sarcoidosis.⁷ It is characterised primarily by non-caseating granulomas and fibrosis in the lung. Symptoms include dyspnoea and dry cough, and chest radiographs show diffuse interstitial fibrosis with or without hilar adenopathy. Pulmonary function testing may reveal either a restrictive or obstructive pattern and/or abnormalities of gaseous exchange. It is essential to test for Be sensitivity as the disease is clinically indistinguishable from sarcoidosis.¹

Exposure to high concentrations of soluble Be compounds, such as sulphate or fluoride, may lead to an

acute dermatitis.⁸ Contact dermatitis involving the face may be associated with conjunctivitis, peri-orbital oedema and upper respiratory tract involvement. Ulceration or granulomatous nodular skin lesions may occur after accidental inoculation of the skin with splinters of Be metal, oxide or crystal and such lesions persist until all the Be material is excised.⁹

The possibility of an immune mechanism for CBD was suggested by the observation that even in the setting of high occupational exposure, the disease only develops in a small percentage of the workforce. It has subsequently been shown that the hypersensitivity to Be triggers a chronic inflammatory response in the lung, mediated by CD4+ T cells. This forms the basis for the beryllium lymphocyte proliferation test (BeLT) used in the screening and diagnosis of Be sensitivity.¹ Research by Richeldi *et al.*¹⁰ has shown that an amino acid substitution on a specific major histocompatibility complex protein was strongly associated with CBD, implicating a genetic risk factor in the aetiology of CBD.

Chromium (Cr)

Chromium is found as metallic Cr or in the trivalent (3+) and hexavalent (6+) states. Trivalent Cr is poorly absorbed through the skin while hexavalent Cr is readily absorbed and acts both as an irritant and sensitizer. Estimates of the prevalence of chrome sensitivity range from 2% of the total population in Finland to as high as 20% in USA populations with dermatitis.¹¹

Although rarely reported, Cr has been implicated in causing asthma in chromium-plating workers. Specific IgE antibody to a Cr human serum conjugate has been demonstrated and this together with a positive response to bronchial provocation testing would suggest a type I immediate hypersensitivity reaction underlying lung-related sensitisation.⁷ Inhalational challenges of chromates in Cr-sensitised workers may produce angioedema, erythema, pruritus, cough, wheezing and bronchospasm.¹³ Clinical reactions may be immediate or late as in asthma.

Cr compounds also produce an allergic contact dermatitis characterised by an acute or chronic eczema which is a classic delayed type IV hypersensitivity reaction. A lag phase of 14 days is necessary for sensitised antigen-specific T-cells to form in the lymphatic system and percolate into the skin. Subsequent dermal exposure causes the release of cytokines and cytotoxic T-cells which produce dermal inflammation.¹³ The effective threshold for elicitation of allergenic contact dermatitis in sensitised populations is 10 ppm (mg/l) of hexavalent Cr in solution.¹¹ Once sensitised however, individuals may present with skin rash within 24 hours of re-exposure.



Acute contact dermatitis.



Acute on chronic contact dermatitis.

Chrome dermatitis has been well described in cement workers where patch testing revealed an 8-9% prevalence of sensitivity although the prevalence of allergic dermatitis is less. In contrast, workers exposed to chromate while handling automobile parts have been shown to have a sensitivity prevalence of 24%. Initiatives to reduce the Cr content of cement have been shown to be successful in reducing the incidence of allergic dermatitis.¹²

Sensitivity to trivalent Cr compounds is rare but patch testing indicates that some workers with Cr sensitivity do react to high concentrations.¹² While chrome is a potent dermal sensitiser and accounts for the most prevalent occupational dermatitis among men, cases of asthma appear to be rare. This discrepancy is thought to be related to the higher propensity for exposure of the skin to different chemical forms of the metal.

Cobalt (Co)

Exposure to Co alone produces an allergic contact dermatitis, rhinitis and occupational asthma while exposure to hard metal dust (tungsten, tungsten carbide and cobalt) produces an interstitial pulmonary fibrosis also known as 'hard-metal disease' of the lung.¹⁴⁻¹⁶

The formation of specific IgE antibodies to protein conjugates of cobalt suggests an IgE-mediated response to workers with occupational asthma due to Co exposure. Among workers exposed to hard metal containing either Co or Ni as a binding matrix both Co-induced and Ni-induced asthma have been described. Immunological mechanisms include IgE-mediated and cell-mediated hypersensitivity and there is ongoing debate around the issue of cross-reactivity between the two metals versus simultaneous sensitisation to both metals in hard-metal asthma.⁷

Atopy (reflected as positive antibodies to common environmental antigens) and age have also been shown to be risk factors for asthma among hard-metal workers.¹³

Hard-metal disease is a pathological process of the pulmonary parenchyma that ranges from intense alveolitis to end-stage pulmonary fibrosis. Episodes of alveolitis are characterised by the acute occurrence of fever, anorexia, cough and dyspnoea with exertion, typically after months to several years of exposure. Symptoms may improve on removal from the workplace but may recur following repeated exposure. Repeat alveolitis may produce interstitial fibrosis. The disease was initially perceived to be one which develops after prolonged exposure to high concentrations of dust from tungsten-carbide-based hard metals that contain Co materials. However, many cases of hard-metal disease

were also diagnosed in diamond polishers who used polishing discs made with Co and the term 'cobalt lung' has been proposed. The mechanism of the pulmonary toxicity of Co has not been elucidated but several features of the condition implicate some form of hypersensitivity or host idiosyncrasy as with chronic Be disease. The absence of a clear dose-response relationship between Co exposure and the development of cobalt lung, together with the fact that very few workers with relatively limited cumulative exposures are affected, supports an immune-mediated aetiology. The known dermal sensitising potential of cobalt and the existence of cobalt-asthma suggests that hypersensitivity to cobalt may cause the fibrosing alveolitis. It is postulated that a cellular hypersensitivity is implicated in the aetiology of hard-metal disease.^{7,14}

Co is one of the three most common metallic sources of contact dermatitis along with Ni and Cr. In the occupational setting, Co-induced contact dermatitis manifests as eczema which occurs commonly on the hands of workers in hard-metal industries. The prevalence of hand eczema in hard-metal factory workers has been estimated to be 10% and risk factors for the development of severe eczema include prior Ni sensitisation and pre-existing irritant dermatitis.

It is thought that sensitisation to these metals occurs as a result of co-exposure to these metals rather than cross-reactivity to them. The diagnosis of Co sensitivity is usually made by patch testing.¹⁴

Mercury (Hg)

Hg is considered a weak sensitiser and research on the effect of occupational exposure has tended to focus on the toxic effects rather than allergic effects of exposure.¹ Contact with Hg salts such as chloride or ammonium chloride may cause hypersensitivity leading to contact dermatitis. Exposure to Hg has been described in the health care setting – antiseptic agents (mercurochrome and thimerosal) and defective medical equipment (thermometers and baumonometers) have the potential to lead to sensitisation, as do amalgam fillings in dental workers.¹⁷ Hg exposure can elicit IgE and IgG formation. Glomerular deposition of IgG complexes is a feature of glomerulopathy and may contribute to the nephrotoxicity of Hg. It is not certain though whether the immune syndromes resulting from Hg exposure are related directly to activation of the immune system or are secondary to Hg-induced tissue damage.⁸

Nickel (Ni)

Ni sensitisation is associated with the development of dermatitis, asthma, rhinosinusitis and possible eosinophilic pneumonia.

From a dermatological perspective nickel is the most common sensitising metal with prevalence rates as high as 29% in patients tending an allergy clinic. In this particular study occupational exposure as a source of sensitisation was suspected in 23% of these patients.¹⁸ In a review of quantitative aspects of skin exposures, threshold values leading to sensitisation have been suggested to be in the range of 0.1-1 $\mu\text{g}/\text{cm}^2$ in occluded skin and 15 $\mu\text{g}/\text{cm}^2$ when non-occluded. Dermal exposure to Ni results in a contact dermatitis which starts with an itchy rash, usually on the hands and the forearms, eventually becoming eczematous.⁸

Once sensitisation occurs, hypersensitivity to nickel usually lasts indefinitely. However long periods of non-exposure tend to diminish the hypersensitivity reaction. Pressure, sweat, moisture and friction increase the hypersensitivity reaction.¹⁸



Subacute contact dermatitis.

Direct effects of Ni inhalation include asthma, chronic hypertrophic rhinitis and sinusitis, nasal polyposis and perforations of the nasal septum.¹⁸⁻²⁰

There is evidence of formation of specific IgE antibodies to protein conjugates of Ni, supporting evidence that asthmatic reaction to this metal is also IgE-mediated.³ Positive inhalational challenge tests to nickel sulphate have been demonstrated in metal-plating workers while lymphocyte transformation tests implicate Ni sensitivity in the development of hard-metal asthma.¹⁸ New evidence has recently emerged from Japan on the potential of Ni to provoke eosinophilic pneumonia. In this case, nickel fumes were inhaled during a training course for welding after which pneumonia confirmed by bronchiolar alveolar lavage (BAL) developed. A subsequent provocation test with nickel sulphate solution caused a recurrence of the pneumonia suggesting an underlying hypersensitivity to Ni.⁷

Cross-reactivity is an important issue in Ni allergy, as Ni exposure often occurs in the context of multiple metal exposures and positive patch tests to other metals (e.g. Co and Cr) are common.⁸

Platinum (Pt)

Occupational asthma and rhinitis caused by Pt salts have been described in workers employed in precious-metal refineries and in industries manufacturing and recycling catalytic converters. Among Pt refinery and Pt catalyst plant workers, occupational asthma persists in a high percentage of subjects even after removal from exposure, and deteriorates with continued exposure even at low levels. Exposure to Pt salts in refinery workers has been associated with elevated IgE levels and in catalyst plant workers with positive skin-prick test reactions to hexachloroplatinic acid solution. 'Platinosis' refers to the development of immediate-type hypersensitivity reactions manifesting as asthma, rhinitis and urticaria and may develop in 50% of exposed workers following provocation with chlorplatinates. Delayed-type hypersensitivity may also occur but has not been proven by large-scale patch testing. Contact dermatitis has been reported secondary to jewellery exposure while contact urticaria has been demonstrated following occupational exposure to the antineoplastic agent cisplatin. Cross-reactivity between Pt and indium and iridium (platinum group metals) has also been observed.^{8,21}

There is good evidence for an IgE-mediated mechanism in Pt salt asthma. Although Pt-specific antibodies have been demonstrated by radioallergen sorbent test (RAST), the consensus is that skin-prick testing is more appropriate for the diagnosis of Pt hypersensitivity.²²

Rhodium (Rh)

Rh, belonging to the same element group as Pt, has been assumed to be as potent as Pt in terms of bronchial and skin sensitisation. A report from Japan suggested that Rh sensitisation occurred in workers who handled Rh replacing Pt as a plating agent.⁶

Zinc (Zn)

While diseases related to Zn exposure are described, little is known about the underlying mechanism causing such disease and no conclusive evidence exists implicating hypersensitivity.

A well-known and relatively benign condition following exposure to metal fumes (mainly zinc oxide) is metal fume fever. This is an influenza-like illness characterised by fever, chills and malaise with relatively mild respiratory symptoms and classically few or no functional or radiographic abnormalities. The symptoms usually start a few hours after exposure and then subside spontaneously. Peripheral leukocytosis is present during the acute illness and studies using BAL have shown marked neutrophil infiltration and cytokine release. The exact pathogenesis of metal fume fever is unknown but an allergic mechanism is suspected and it has been postulated that the condition may be superimposed on asthma or hypersensitivity pneumonitis.²² There are rare reports of asthma in subjects welding galvanised metal who present with positive bronchial challenge tests and a case of hypersensitivity pneumonitis in a worker exposed to Zn fumes in a smelter has also been reported.⁷

Zirconium (Zr)

Zr may cause granulomas in human skin, but has not been associated with granulomatous or fibrotic lung disease. A delayed-hypersensitivity reaction is thought to cause the cutaneous reaction to Zr.^{2,7}

An approach to the diagnosis and management of allergic disease following sensitisation to metal

The diagnosis of metal-induced allergic diseases, as with other occupational diseases, is dependent on the level of knowledge of the physician who first sees the patient. Awareness of the sensitisation potential of certain metals is the first step in the recognition of metal-induced allergic disease and requires that a proper occupational history be taken. This needs to include information about the patient's occupation, the exposure to sensitising metals and the conditions under which such exposure occurs.

A detailed history of the presenting complaint and the clinical course of the condition needs to be elicited. It must be emphasised that symptoms are not specific for metal-induced allergic disease and the role of metal sensitisation in the aetiology may easily be missed. Factors supporting a diagnosis of metal-induced allergic disease in the occupational setting include:

- Exposure to a metal known to have sensitising potential in the workplace
- Symptoms that commence after an initial latency period following exposure to a sensitising metal
- Symptoms that are triggered by exposure to or contact with sensitising metals with clinical improvement when exposure ceases
- Triggering of symptoms on re-exposure to the metallic antigen after a period of non-exposure
- Increased sensitivity with hypersensitivity reactions occurring at lower concentrations of the sensitising metal than previously encountered

- Worsening of symptoms and clinical condition with ongoing or increased exposure
- Symptoms that are compatible with disease known to be immune-mediated such as asthma, contact dermatitis, urticaria, rhinitis, etc
- Objective evidence of sensitisation such as a positive RAST, skin-prick test or patch test.

The diagnosis of metal-induced allergic diseases may be supported by the use of allergological tests. The choice of test depends on the clinical presentation. Manifestation of type I reactions such as asthma and urticaria may be confirmed with skin-prick test to metal antigen, as with Pt salts, or the presence of specific antibody demonstrated with RAST, as with Co, Ni and Cr. Bronchial provocation with the suspected sensitizer under controlled conditions may support a diagnosis of hypersensitivity in allergic asthma. Hypersensitivity reactions which are cell-mediated such as contact dermatitis are best demonstrated by using patch testing, as with Ni and Cr contact dermatitis. The lymphocyte transformation test has also been used for the diagnosis of metal-induced granulomatous and fibrotic lung disease. Since BAL may contain more lymphocytes responding to metal antigens than peripheral lymphocytes, it is increasingly being used in interstitial lung disease such as fibrosing alveolitis secondary to cobalt exposure and in CBD following Be exposure.⁷

While exposure control should be a priority in the prevention of metal-induced allergic disease, this is very difficult in a setting of poor exposure characterisation, a lack of knowledge about the potentially harmful effects on health and the lack of exposure standards based on epidemiological studies.⁷ Follow-up studies of occupational asthma cases suggest that total removal of symptomatic workers from further exposure is required to prevent permanent asthma.⁶ It is reasonable to adopt the same approach for asthma due to metal sensitisation. Similarly, the mainstay of treatment in contact dermatitis is avoidance of the sensitising metal. This may be achieved through a change in work practices or through the wearing of appropriate personal protective equipment such as gloves to decrease contact.

For prevention to be effective there needs to be a greater awareness of the sensitising potential of metals in the workplace. This will require that employers and workers receive education about the effects on health, the need to adopt safe work practices and the implementation of environmental controls to limit exposure. Surveillance of workers' health by means of periodic and risk-based screening programmes may also be indicated in industries where the potential for sensitisation is high. This will aid the early detection of sensitised individuals and limit the impact on health of exposed workers.

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