9.20 Toxicity of Airborne Metals

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Abstract

Metals and their compounds are persistent in the environment and originate from multiple sources. Some metals are essential for the human body while others, such as cadmium and arsenic, are known carcinogens. Health effects associated with the acute or chronic inhalation of airborne metals remains an area of intense research interest, especially for mixtures. Inhalation is a primary route of exposure to metals and occurs in the workplace and in the environment. This chapter provides public health officials, physicians, toxicologists, and others with an overview of the major components involved in the respiratory toxicology of airborne metals. General health effects associated with metal inhalation, risk factors associated with environmental and occupational exposures, and pulmonary deposition and handling will be discussed.

9.20.1 Introduction

This section focuses on the respiratory effects of inhaled metals. Other routes of exposure, such as dermal and ingestion, are covered in other chapters. For certain metals, the route of exposure can determine toxicity and exposure via the oral or dermal routes can result in pulmonary toxicity absent inhalation exposure. The respiratory toxicity associated with inhaled metals is a broad topic that cannot be covered in-depth for all metals in a single section. For simplicity and to provide a general appreciation of inhaled metal toxicity, this section is divided into four subsections: 1) Highlighted Metals and Primary Toxicities, 2) Exposure, 3) Pulmonary Deposition and Handling, and 4) Inhaled Metal-associated Health Effects. The health effects section discusses general mechanisms.

Understanding risks of metals requires an integration of information across the entire risk paradigm, including sources and emissions, air quality, exposure (the contact of a person with the metal over a particular duration of time), dose (the amount retained in the respiratory tract), and effects (noncancer and cancer). Environmental and occupational are the most likely sources of inhalation metal exposure. Typically, occupational exposure results in significant exposures to specific metals at air concentrations higher than typical environmental exposures seen by the general population. This section begins with an overview of known metal toxicities with an emphasis on inhalation. The subsequent sections summarize source of exposure, pulmonary handling, and resultant health effects from a mechanistic perspective.

9.20.2 Highlighted Metals and Primary Toxicities

Regardless of environmental or occupational exposure, virtually all metals have the potential to be inhaled and cause pulmonary injury. The health effects and toxicological profiles of the following metals of occupational and environmental importance are summarized: antimony (Sb), arsenic (As), beryllium (Be), cadmium (Cd), chromium (Cr), cobalt (Co), lead (Pb), manganese (Mn), mercury (Hg), nickel (Ni), selenium (Se), iron (Fe), copper (Cu), zinc (Zn), tin (Sn), aluminum (Al), indium (In), silver (Ag), and uranium (U). These metals include the profile of metals designated as hazardous air pollutants by the EPA including antimony, arsenic, beryllium, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, and selenium (EPA HAP, 2023). Metals including arsenic, cadmium, chromium, beryllium, and nickel which are recognized by The International Agency for Research on Cancer (IARC, 2023) as carcinogens most important to air toxics regulation (Straif *et al.*, 2010). The list also includes major metal hazards found in the dust of primary metal industries by the Occupational Safety and Health Administration (OSHA, 2023), including iron, aluminum, manganese, beryllium, cadmium, tin, copper, silver, nickel, and lead (OSHA, 2011). Additional metal pollutants such as zinc and uranium were also included. Additional information on the toxicity of these and other inhaled metals can be found here (Balali-Mood *et al.*, 2021; Egorova and Ananikov, 2017; Nordberg and Costa, 2021a,b; Tchounwou *et al.*, 2012; ATSDR Tox Profiles, 2023; ATSDR ToxGuides, 2023; EPA Fact Sheets, 2023; EPA HAP, 2023; EPA IRIS, 2023; EU-OSHA, 2023; IARC, 2023; NIOSH NPG, 2023; OSHA, 2023; Wu *et al.*, 2016)

9.20.2.1 Antimony (Sb)

Antimony, a metalloid, in its various forms is present naturally in the earth's crust and in ambient air is ~1 ng/m^3 (ATSDR ToxGuides, 2023). OSHA permissible exposure limit (PEL) and NIOSH recommended exposure limit (REL) for antimony and its compounds is 0.5 milligrams per cubic meter of air (mg/m³) as a time-weighted average (TWA) concentration over an 8-hour work shift (NIOSH NPG, 2023). Antimony exposure is higher in occupational settings and the environment around processing sites. Antimony is used in many industries. It has applications in semiconductors, infrared detectors, diodes, and batteries; it is also used to make flame-retardant materials. The primary routes of exposure are pulmonary and dermal. Animal inhalation studies found high acute toxicity in the lung, cardiovascular system, and liver. Acute dermal exposure is known to cause a rash known as "antimony spots." Ocular exposure causes conjunctivitis and exposure through ingestion is known to cause gastrointestinal effects, including abdominal pain and persistent anorexia in humans. Chronic inhalation exposure in humans causes pneumoconiosis, chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesion, alteration in pulmonary function and cardiovascular effects. EPA has not classified antimony for carcinogenicity (EPA IRIS, 2023). IARC classified trivalent antimony as probably carcinogenic to humans (Group 2A) and pentavalent antimony as not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 2023).

9.20.2.2 Arsenic (As)

Arsenic is a metalloid and widely distributed throughout the environment in air, water, and soil. The inorganic form is associated with greater toxicity and severe health effects. The common route of exposure for arsine is inhalation, while the common route of exposure for inorganic arsenic is ingestion of contaminated drinking water. Occupational exposure through inhalation at higher doses occurs as it is used widely as a wood preservative and in paints and pesticides. Arsenic exposure affects many organs including the eyes, skin, liver, kidneys, lungs, and lymphatic system. Arsine is present in ambient air 1–3 ng/m^3 in rural locations and 20–100 ng/m^3 in urban locations. In the U.S. it is present in drinking water at 2 μg/L on average (ATSDR ToxGuides, 2023). EPA has set a limit of 0.01 ppm for arsenic in drinking water but has no ambient air standard (i.e., no general air pollution limit) for arsenic (EPA Fact Sheets, 2023). OSHA PEL for arsenic is 10 μg/m³ for an 8-hour shift. NIOSH REL for arsenic is 2 μg/m³ (NIOSH NPG, 2023). Arsenic, irrespective of the route of exposure, once absorbed is distributed by the blood throughout the body. Acute inhalation exposure causes gastrointestinal effects, central and peripheral nervous system disorders. Acute ingestion exposure can result in mortality and lower level of exposure can affect the gastrointestinal tract (nausea, vomiting), central nervous system (CNS) (headaches, weakness, delirium), cardiovascular system (hypotension, shock), and blood (anemia, leukopenia) (EPA Fact Sheets, 2023). Chronic inhalation exposure is known to cause skin lesions, cardiovascular disorders, and nerve damage. Chronic oral exposure causes skin lesions, pigmentation change, hyperkeratosis, gastrointestinal system, blood, liver, and kidney damage. Reproductive and developmental effects also result from arsenic exposure including spontaneous abortion rates in women, birth defects, and cognitive and neurobehavioral deficits. IARC has determined that arsenic and inorganic arsenic as carcinogenic to humans (Group 1) (IARC, 2023). EPA also has classified inorganic arsenic as a known human carcinogen (EPA IRIS, 2023).

9.20.2.3 Beryllium (Be)

Beryllium and its metal alloys are used widely in electronic components. Beryllium exposure is higher in occupational settings and in environments around processing sites. In ambient air, beryllium is present at 0.0001–8.9 ng/m^3 and in surface water 0–32.6 μg/L (ATSDR ToxGuides, 2023). OSHA PEL for beryllium and beryllium compounds is TWA 0.2 μg/m³. NIOSH REL for beryllium is 0.5 μg/m^3. Inhalation is the major route of exposure (NIOSH NPG, 2023). Acute exposure of beryllium causes acute pneumonitis (inflammation of the lung) and is reversible. Acute dermal exposure results in skin allergy and acute conjunctivitis. Chronic inhalation exposure causes chronic pneumonitis, immunological effects, reduced lung capacity, shortness of breath, fatigue, anorexia and "berylliosis", a disease that causes non-cancerous granulomatous lesions in in the lung (Sizar and Talati, 2022). Reproductive and developmental effects were not reported. IARC has classified beryllium and beryllium compounds as carcinogenic to humans (Group 1) (IARC, 2023). EPA also has classified beryllium as a probable human carcinogen to humans when exposed through inhalation (EPA IRIS, 2023).

9.20.2.4 Cadmium (Cd)

The main source of the heavy metal cadmium in air is through burning of fossil fuels, municipal waste incineration and as byproduct in nonferrous metal smelters. Cadmium levels in ambient air range from 0.1–5 ng/m^3 in rural areas, 2–15 ng/m^3 in urban areas, and 15–150 ng/m^3 in industrialized areas (ATSDR ToxGuides, 2023). OSHA PEL for all cadmium compounds is TWA 5 μg/m^3 (NIOSH NPG, 2023). Inhalation and ingestion are two main routes of cadmium exposure. Acute inhalation exposure can result in lung irritation and functional impairment. Chronic inhalation exposure can lead to bronchiolitis, emphysema, kidney problems including kidney failure and mortality. Chronic cadmium exposure caused "Itai-itai" disease in Japan (Nordberg *et al.*, 2015). This disease causes accumulation of cadmium in the liver and kidney followed by musculoskeletal damage and bone deformities. Cadmium exposure results in reproductive and developmental effects including decreased birthweights and reduction in sperm number (ATSDR Tox Profiles, 2023). Cadmium can bind to estrogen receptors and mimic the actions of estrogen (Aquino *et al.*, 2012). IARC classified cadmium and cadmium compounds as carcinogenic to humans (Group 1) (IARC, 2023). EPA also has classified cadmium as a probable human carcinogen (EPA IRIS, 2023).

9.20.2.5 Chromium (Cr)

Chromium exists as chromium (III) or chromium (VI) and in a less common metallic chromium (Cr 0) form. The trivalent chromium (III) valence state is less toxic than the hexavalent state chromium (VI). Chromium (III) is an essential nutrient to the body and at low exposures it can convert chromium (VI) to chromium (III). The primary routes of exposure to chromium include inhalation, ingestion, and dermal. OSHA PEL for Cr (VI) is TWA 5 μg/m³ and NIOSH REL for Cr (VI) is 0.2 μg/m³. OSHA PEL for Cr (III) compounds is TWA 0.5 mg/m³ and NIOSH REL for Cr (III) is 0.5 mg/m³. OSHA PEL for chromium metal is 1 mg/m^3 and NIOSH REL is 0.5 mg/m^3 (NIOSH NPG, 2023). Ambient air concentration of chromium is <20 ng/m^3 and a major portion of it is in the chromium (III) form (ATSDR ToxGuides, 2023). Chromium in mixed valence states and at higher concentrations is found in occupational settings and in environments around processing sites including tanning, chromate production, stainless-steel production, chrome plating, welding, and thermal spray coating. Although information on health effects after acute exposure for chromium (III) is lacking, acute exposure to high levels of chromium (VI) causes pulmonary irritation, gastrointestinal, and

neurological effects. Chronic chromium (VI) exposure by inhalation is known to cause perforations and ulcerations of the septum, bronchitis, decreased pulmonary function, pneumonia, asthma, and nasal itching. Depending on the dose, other systemic organs including the liver, kidney, gastrointestinal, and immune systems were also found to be affected. Dermal exposure can lead to ulceration of the skin, sensitivity, and dermatitis. Exposure to chromium (VI) by inhalation may result in complications during pregnancy and childbirth. No definitive reproductive and developmental issues have been reported for other forms of chromium. IARC determined chromium (VI) as carcinogenic to humans (Group 1). Chromium (III) and metallic chromium were determined as not classifiable as to their carcinogenicity to humans (Group 3) (IARC, 2023). EPA has classified chromium (VI) as a known human carcinogen when exposure occurs through inhalation (EPA IRIS, 2023).

9.20.2.6 Cobalt (Co)

Cobalt is an essential metal to the human body and is part of vitamin B12. Cobalt is used in alloys that need to maintain strength at high temperatures such as grinding and cutting tools. It is also used as a pigment, in medical implants and in batteries. Ambient level of cobalt in air is 0.025–2.2 ng/m^3 (ATSDR ToxGuides, 2023). Except in occupational settings like hard metal industrial sites, cobalt exposure is higher through ingestion than from inhalation. OSHA PEL for cobalt is TWA 0.1 mg/m³. NIOSH REL for cobalt is TWA 0.05 mg/m^3 (NIOSH NPG, 2023). Acute inhalation exposure causes lung hemorrhage, edema, and decreases in ventilatory function. Chronic exposure can lead to decreases in lung function, sensitization leading to asthma, pneumonia, and fibrosis. Animal studies indicated inhalation exposure apart from lung, affected cardiovascular system, central nervous system (CNS), liver, and kidney. EPA has not classified cobalt for carcinogenicity (EPA IRIS, 2023). IARC determined cobalt metal and soluble cobalt (II) salts were probably carcinogenic to humans (Group 2A). Cobalt(II) oxide was classified as possibly carcinogenic to humans (Group 2B)(IARC, 2023).

9.20.2.7 Lead (Pb)

Lead in its various forms is widely used in ammunition, jewelry, pigments, batteries, aviation fuel, cable sheathing, pipe and plumbing materials. Ambient air levels of lead in 2008–2010 was 200 ng/m^3 (ATSDR ToxGuides, 2023). Lead concentrations in air have drastically dropped since its ban from use in consumer paints and as a gasoline additive. Toxicity from lead is primarily caused by persistence and potential for bioaccumulation. Common sources of high dose exposure to lead are ingestion followed by inhalation. OSHA PEL and NIOSH REL for lead is TWA 50 μg/m^3 (NIOSH NPG, 2023). Acute exposure can lead to brain damage, kidney damage, and gastrointestinal distress. Lead is known to accumulate in teeth and bones. Lead exposure can also cause renal impairment, anemia, immunotoxicity, and chronic kidney disease. Reproductive and developmental problems including decreased sperm count, spontaneous abortions, low birth weight, slowed postnatal neurobehavioral development also may occur with exposure. Children are especially susceptible and lead exposure is known to cause severe neurological and developmental challenges in children. EPA classified lead as a probable human carcinogen (EPA IRIS, 2023). IARC classified lead as possibly carcinogenic to humans (Group 2B) (IARC, 2023).

9.20.2.8 Manganese (Mn)

Manganese (Mn) is a trace element that is present naturally in various foods and is an essential nutrient required for activation of various enzymes. It is used in fireworks, various metal alloys, batteries, fertilizers, catalysts, as a gasoline additive, and in the welding industry. Inhalation is the primary route of exposure. Inhalation of high doses of manganese is predominant in occupational settings and in environments around processing sites including iron and steel production plants, power plants, and coke ovens. Ambient levels of manganese in urban air is 40 ng/m^3 and <10 ng/m^3 in rural areas (ATSDR ToxGuides, 2023). OSHA PEL is TWA 5 mg/m³ and NIOSH REL is 1 mg/m^3(NIOSH NPG, 2023). Acute high dose exposure to manganese causes respiratory effects including cough, bronchitis, difficulty breathing during exercise, and an increased susceptibility to infectious lung disease. Inhaled manganese is transported to the brain. Chronic exposure causes a neurological disorder called "manganism." The symptoms of this disease are tremors, difficulty walking, and facial muscle spasms (Racette, 2014). Epidemiological studies also reported other effects related to the nervous system including slower visual reaction time, poorer hand steadiness, and impaired eye-hand coordination. Male workers exposed to high level of manganese reported impotence and loss of libido. EPA classified manganese as not classifiable as to human carcinogenicity (EPA IRIS, 2023). IARC has not evaluated manganese for carcinogenicity (IARC, 2023).

9.20.2.9 Mercury (Hg)

Mercury is used in many industries including construction, electrical, maritime, chemical, and mining. It is also used in medical equipment and in dental amalgams. Mercury is present in three forms, metallic elemental mercury, inorganic mercurial salts (e.g., $HgCl_2$), and as organic mercurials (e.g., methylmercury). Ingestion is the primary route of exposure to organic mercurials. Inhalation is the primary route for metallic elemental mercury and occurs when it is in vapor form. Inhaled vapor is almost completely absorbed by the lungs about up to 80%. In 2019, the mean mercury levels in U.S. ambient air is 1.11–2.22 ng/m^3 (ATSDR ToxGuides, 2023). OSHA PEL for mercury vapors is TWA 0.1 mg/m³. NIOSH REL for mercury is 0.05 mg/m^3 (NIOSH NPG, 2023). High dose mercury exposure can cause adverse renal effects (due to bioaccumulation), respiratory failure, and death.

It may also cause a severe neurological disease called "Minamata disease" (Eto, 2000). Patients with this disease manifest intellectual disability, disturbance of coordination, deformities of the limbs, poor reflexes, poor nutrition, and impaired growth. Mercury exposure causes alterations in testicular tissue and abnormalities in fetus development. EPA determined mercury as not classifiable as to its human carcinogenicity. EPA classified inorganic and methyl mercury as a possible human carcinogen (EPA IRIS, 2023). IARC classified mercury and inorganic mercury compounds as not classifiable as to its carcinogenicity to humans (Group 3) and methylmercury as possibly carcinogenic to humans (Group 2B) (IARC, 2023).

9.20.2.10 Nickel (Ni)

Nickel resists corrosion and, therefore, is used in making batteries, jewelry, gas turbines, rocket engines, and alloys like stainless steel; it is also used in electroplating and as a catalyst in industrial carbonylation reactions. It has wide scale applications in chemical, marine, aeronautical, and oil industries and in consumer products. Nickel exposure occurs through ingestion, dermal, and inhalation routes. Inhalation is the predominant route of exposure in occupational settings and in environments surrounding nickel processing industries. The mean concentration of nickel in ambient air in the U.S is 2.22 ng/m^3 (ATSDR ToxGuides, 2023). OSHA PEL for nickel is TWA 1 mg/m^3. NIOSH REL for nickel is 0.015 mg/m^3 (NIOSH NPG, 2023). Nickel can cause dermal hypersensitivity and contact dermatitis. Acute exposure can cause respiratory tract irritation, pulmonary fibrosis, and renal edema. Chronic exposure leads to sinusitis, occupational asthma, and dermatitis. The pulmonary health effects and toxicity of nickel including pulmonary inflammation were generally associated with the rate of solubility of the nickel form. The potential for nickel to induce reproductive effects has not been firmly established, but some animal studies report effects on the male reproductive system. IARC classified metallic nickel as possibly carcinogenic (Group 2B) and nickel compounds as carcinogenic to humans (Group 1) (IARC, 2023). Nickel refinery dust and nickel subsulfide are classified by the EPA as human carcinogens, and nickel carbonyl is classified as a probable human carcinogen (EPA IRIS, 2023).

9.20.2.11 Selenium (Se)

Selenium is an essential micronutrient and is required for activation of several enzymes such as glutathione peroxidase. It is used as nutritional supplement and as a feed additive for poultry and livestock. It is used as a catalyst in pharmaceutical industry. Being a semiconductor is used extensively in the electronic industry. OSHA PEL and NIOSH REL for selenium and its compounds is 0.2 mg/m^3. Selenium is present at a low concentration in ambient air and is generally <10 ng/m^3 (ATSDR ToxGuides, 2023). Selenium is present at high concentrations (up to 950 μg/m^3) in air at occupational settings and in environments around the processing plants. Occupational inhalation exposure to selenium vapors may cause dizziness, fatigue, irritation of mucous membranes, and respiratory effects. High dose exposure to selenium was found to cause neurological effects, lack of mental alertness, discoloration of skin, tooth decay, loss and deformation of hair and nails. No information is available on the developmental or reproductive effects of selenium in humans. Epidemiology studies found inverse association between selenium levels and cancer occurrence. IARC determined selenium and selenium compounds as not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 2023). EPA has classified elemental selenium as not classifiable as to human carcinogenicity and selenium sulfide as a probable human carcinogen (EPA IRIS, 2023).

9.20.2.12 Iron (Fe)

Iron is an essential nutrient that plays an important role in various cellular processes including oxygen transport and deoxyribonucleic acid (DNA) synthesis. Because iron is the most widely used metal, exposure can occur in many industrial sectors, including construction, metal processing, automobile, and transportation. Iron is the most abundant metal in air pollution particulate matter. It is present at high levels in occupational settings like metal foundries and in other environments like subway stations. Iron levels in ambient air in New York City subways were found to range from 141–329 μg/m^3 (Luglio David *et al.*, 2021). In Beijing, iron in ambient air ranged from 0.378–0.614 μg/m^3 based on the season (Chen *et al.*, 2017). NIOSH REL for iron oxide dust and fume is TWA 5 mg/m^3 and OSHA PEL for iron oxide dust and fume is TWA 10 mg/m^3. NIOSH REL for other forms of iron salts is TWA 1 mg/m^3 (NIOSH NPG, 2023). Excess iron deposits in the lung causes a benign condition known as pulmonary siderosis or Welder's disease, a form of pneumoconiosis (Doherty *et al.*, 2004). Iron dyshomeostasis has been implicated in neurodevelopmental disorders including autism, schizophrenia, and attention deficit disorder. Iron is known to cause low birth weight. The precise mechanisms are unknown, but iron is thought to induce health effects by generation of reactive oxygen species through the Fenton rection which causes imbalances in the oxidative stress cycle. Iron exposure interferes with phosphorus assimilation and causes severe rickets in infants. IARC classified occupational exposures during iron and steel founding and hematite underground mining as carcinogenic to humans (Group 1) and iron oxides are not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 2023). EPA concluded that the available data is inadequate for an assessment of the human carcinogenic potential of inhaled iron oxide (EPA, 2006). Iron will be discussed later in the chapter as its involvement in inducing cancer and neurological toxicity is an emerging area of research.

9.20.2.13 Copper (Cu)

Copper, an essential metal for the human body, is present at high concentrations in brain, liver and kidney. Copper homeostasis is tightly regulated and required for processes such as protein synthesis and antioxidant defense. Wilson's disease is a genetic disorder that dysregulates homeostasis and causes copper build-up and subsequent organ failure. Copper is used in wiring, plumbing, pesticides, cookware, and dietary supplements. Ambient air levels are in the mean range of 20–790 ng/m^3 (ATSDR ToxGuides, 2023) Copper is present at high concentrations in air at occupational settings including smelters, recycling plants, and copper metal processing sites. OSHA PEL and NIOSH REL for copper (dusts and mists) is TWA 1 mg/m^3. OSHA PEL and NIOSH REL for copper fume is TWA 0.1 mg/m^3 (NIOSH NPG, 2023). Acute exposure to copper can cause metal fume fever, an illness with flu-like symptoms. Depending on the dose it can also cause irritation of nasal mucous membranes, eye irritation, and upper respiratory tract irritation. Chronic exposure to copper can damage the liver and kidneys. Agricultural workers in Portugal exposed to copper sulfate for 2–15 years showed Vineyard sprayer's lung disease. Patients with this disease have decreased lung function, progressive massive fibrosis, and interstitial pulmonary lesions. EPA classified copper as not classifiable as to human carcinogenicity. IARC has not evaluated the carcinogenicity of copper.

9.20.2.14 Zinc (Zn)

Zinc is an essential metal and plays an important role in the production and activation of several enzymes in the human body. Zinc and zinc compounds have wide applications including use as coating to prevent rust, in alloys for welding, for making currency, as a wood preservative; it is also used in dry cell batteries, paint, rubber and medicine. Average concentration of zinc in ambient air in the U.S. is 20–160 ng/m^3 for urban areas and 10–50 ng/m^3 for rural areas (ATSDR ToxGuides, 2023). Inhalation is the primary route of exposure in occupational settings and occurs at facilities producing fabricated metal products or processing zinc. Inhalation of zinc dust can lead to increase in blood Zn levels due to dissolution and diffusion. Apart from lung injury and inflammation, the zinc ions can cause cardiovascular blood coagulation impairments and injury to renal organs. Acute high dose exposure to zinc causes metal fume fever with symptoms including fever, chills, aches, cough and chest tightness. NIOSH REL and OSHA PEL for zinc oxide is TWA 5 mg/m³ (NIOSH NPG, 2023). There are no human reports of reproductive and developmental effects due to zinc exposure. EPA has determined zinc as not classifiable as to human carcinogenicity. IARC has not classified zinc for carcinogenicity.

9.20.2.15 Tin (Sn)

Tin exists in metallic, inorganic, and organic forms. Metallic tin is used as can liner for food and beverages. Inorganic tin forms are used in dyes, food additives, soaps, and toothpaste. The organic form is used as a stabilizer in plastics, as a biocide and in lithium-ion batteries. There are negligible levels of tin in ambient air except in occupational settings. OSHA PEL and NIOSH REL for metallic and inorganic tin is TWA 2 mg/m^3. OSHA PEL and NIOSH REL for organic tin form is TWA 0.1 mg/m^3 (NIOSH NPG, 2023). Exposure to tin can cause nasal and pulmonary irritation, coughing, inflammation, and shortness of breath. The organic forms of tin are more toxic than the metallic and inorganic forms. The inorganic form of tin doesn't bioaccumulate and leaves the body very quickly (ATSDR Tox Profiles, 2023). Organotin exposure can affect the brain, nervous system, immune system, and in severe cases cause death. Tin oxide deposited in the lung tissue after inhalation in occupational settings involving tinning, tin-working, and smelting causes "Stannosis", a non-fibrotic form of pneumoconiosis (Robertson *et al.*, 1961). Animal studies found organotin exposure can affect the reproductive system. Animal studies found inorganic tins not to be carcinogenic and some forms of organic tins to be carcinogenic. EPA and IARC have not classified metallic tin or inorganic tin compounds for carcinogenicity. The EPA has determined that a specific organotin, tributyltin oxide, is not classifiable as to human carcinogenicity (EPA IRIS, 2023).

9.20.2.16 Aluminum (Al)

Aluminum is the third most abundant element in the earth's crust. It is designated as GRAS (Generally Recognized as Safe) by the FDA. Occupationally, workers may be exposed to high levels of aluminum by inhalation in fabricating and processing industries such as welding, aircraft, automotive, and consumer products including utensils, flat screen TVs, laptops, tablets, and smartphones. Aluminum is used as an adjuvant for a major portion of vaccines and is used in various pharmaceuticals including antacids and antidiarrheal agents. Average levels of aluminum in ambient air ranges between 0.005–0.18 μg/m^3. In occupational environments and in urban areas it ranges between 0.4–8.0 μg/m^3 (ATSDR ToxGuides, 2023). NIOSH REL for aluminum is TWA 10 mg/m^3 and OSHA PEL is TWA 15 mg/m^3. NIOSH REL for soluble aluminum salts is TWA 2 mg/m^3 (NIOSH NPG, 2023). Aluminum exposure causes decreases in lung function, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, pneumoconiosis, alveolar proteinosis, and interstitial pneumonia. The decrease in pulmonary function also results in cardiovascular effects. Studies found associations between aluminum inhalation exposure and the risk of Alzheimer's disease (Campbell, 2002). There is a significant correlation between exposure dose and neurological effects including decrease in memory and lag in reaction-time. Exposure to high doses causes aluminum to bind to proteins resulting in glomerular filtration failure and nephrotoxicity. IARC has classified

occupational exposures during aluminum production as carcinogenic to humans (Group 1) (IARC, 2023). EPA has not evaluated the carcinogenic potential of aluminum in humans.

9.20.2.17 Indium (In)

Indium is a rare earth metal and is produced mainly from zinc ore processing. It can also be found in small amounts in iron, lead, and copper ores. As an alloy with tin forms indium-tin oxide (ITO), a transparent and conductive material used in optoelectronics like liquid crystal displays that are used in mobiles, laptops, televisions, and various digital screens. Indium is also used as a coating in high performance engines and in fire sprinklers. Indium is present in negligible levels in ambient air. Primary exposure to indium is through inhalation in occupational settings including ITO manufacturing, processing, and reclamation industries. Indium is known to accumulate in lungs and has slow clearance. Indium exposure in workers causes 'indium lung disease' characterized by pulmonary alveolar proteinosis that can progress quickly to fibrosis with or without emphysema (Cummings *et al.*, 2012). NIOSH REL for indium is TWA 0.1 mg/m^3 (NIOSH NPG, 2023). IARC has determined indium tin oxide as possibly carcinogenic to humans (Group 2B) and indium phosphide as probably carcinogenic to humans (Group 2A) (IARC, 2023). EPA has not evaluated the carcinogenic potential of indium in humans.

9.20.2.18 Silver (Ag)

Silver is present in ambient air at negligible levels (< 1 ng/m^3). High level inhalation exposure occurs in factories that manufacture or utilize silver compounds such as in jewelry making, soldering, and analog photography. Acute silver exposure can cause lung and throat irritation, difficulty breathing, and gastrointestinal effects. Some forms of silver are known to cause liver bile duct hyperplasia (NIOSH, 2021). High-dose exposure through ingestion or inhalation is known to cause argyria, a condition in which a patient's skin and other body tissues turn gray or blue-gray (Drake and Hazelwood, 2005). Argyria, while permanent, is mostly considered a cosmetic condition. NIOSH REL and OSHA PEL for metal and soluble forms of silver is TWA 0.01 mg/m^3 (NIOSH NPG, 2023). EPA has determined silver as not classifiable as to human carcinogenicity.

9.20.2.19 Uranium (U)

Uranium is a naturally occurring radioactive heavy metal. The highly enriched form of uranium is used for nuclear power generation and nuclear weapons. The low enriched form is used for medical applications including treating various types of cancers, AIDS, and certain types of anemia. Due to its high density, depleted uranium is used as a radiation shield, as a counterweight in aircrafts, and in armor-piercing bullets. Uranium is naturally present in many soils with higher concentrations found in the western United States. Very low levels (attocurie/m^3 range) of uranium are found in the ambient air. Exposure occurs through inhalation of the dust from legacy uranium mine sites (Zychowski *et al.*, 2018) and occupational settings involving uranium mining, milling, and processing operations (ATSDR Tox Profiles, 2023; Brugge and Buchner, 2011). These sites have uranium in picocuries per liter range. Apart from radiation-induced health hazards, high dose exposure can result in pulmonary failure, cardiovascular dysfunction, and kidney damage manifested by glomerular and tubular wall degeneration. NIOSH REL and OSHA PEL for soluble uranium compounds is TWA 0.05 mg/m³. NIOSH REL and OSHA PEL for the metallic and insoluble forms of uranium is TWA 0.2 mg/m³ (NIOSH NPG, 2023). IARC determined uranium and its various mixture of isotopes as carcinogenic to humans (Group 1) (IARC, 2023).

9.20.3 Exposure

In a simplistic fashion, the risk of a specific substance can be defined as the product of hazard and exposure. Therefore, to confer risk, an exposure is needed. As stated previously, exposures can be from multiple pathways and all pathways are considered in a risk assessment. The content of these sections will consider primarily inhalation as the route of exposure. Knowing sources, such as environmental or occupational, also provides clues to identifying potential populations at risk and identifying mitigation options.

9.20.3.1 Sources

Metals are widely distributed in the environment, and the potential for airborne exposure, either at the workplace or in ambient air, may be significant. Metals enter the air from both natural processes and anthropogenic sources. Small amounts enter the environment through natural weathering of minerals, entrainment of dust particles, volcanic eruptions, and other natural phenomena; however, most are released through human activities.

Combustion processes and the extensive use of metals in various industrial and agricultural activities and consumer products can result in widespread human exposure (Bachmann *et al.*, 1996; EPA, 2004, EPA HAP, 2023; EU-OSHA, 2023; OSHA). Major industrial sources of metal emissions include both primary and secondary metal production (e.g., refineries, chemical plants, smelters, and mining operations). Dust particles, fine and ultrafine, and fumes are associated with metallurgic operations and with

workplaces where there is crushing and grinding, welding, soldering, and painting. Metals also enter the air from certain industrial processes, such as ceramic and pigment production. Fossil fuel combustion and waste incineration also result in significant atmospheric emissions.

Inhalation exposure to complex metal mixtures (discussed in a later section) also occurs from mining and smelting operations (Csavina *et al.*, 2012, 2014). Mining operations are notable with respect to the quantity of metal containing dusts generated. Most of the metal mining and processing in the world occurs in arid and semiarid environments. The low humidity and strong winds found in the arid regions, like the U.S. Southwest, make respirable dust levels potentially problematic. Dust from mine tailings is an especially serious concern in arid and semiarid regions throughout the world due to the increased susceptibility to windborne transport of metal-laden dust particles. This issue can be particularly acute just downwind from mine tailings and smelter sites, where dusts can contain high levels of metal(loid)s, with adverse health outcomes following inhalation exposures (Csavina *et al.*, 2011). The relative levels of metals in aerosols from mining operations and potential for inhalation exposure depends on the aerodynamic diameter (Gonzales *et al.*, 2014). For example, samples collected at an active mining and smelting site showed the highest levels of arsenic, lead, and cadmium in the fine particulate (0.1–1.0 μm) meaning inhalation to the deep regions of the lung is possible.

Nanotechnology has resulted in the manufacture of nanosized (i.e., one physical dimension < 0.1 μm) metals with unique properties. The global nanotechnology market size, which includes nanometals, is in the billions and is continually expanding at a significant rate. With that, workers and consumers have the potential to be exposed. The engineered nanometals can be individual metals of various sizes or made into fibers/wires/nanobelts potentially altering the mechanism of toxicity. Metal oxides exhibit critical sizes for which new material properties emerge when compared to bulk scale materials, including changes in lattice structure and crystallinity, optical and electronic band gap properties, phase transformations, photocatalytic activity, adsorptive capacity, and redox activity (Auffan *et al.*, 2009). For example, gold nanoparticles below 2 nm exhibit redox catalytical activity that is not present at larger sizes (Turner *et al.*, 2008) and the phototoxicity of TiO_2 is influenced by particle size (Xiong *et al.*, 2013).

As the nominal size of a metal decreases, the surface area per unit mass increases. This simply means for a given unit of mass, there will be many more nanosized metal particles compared to fine sized metals. For titanium dioxide, ultrafine TiO_2 caused significantly more pulmonary inflammation and injury compared to an equal mass dose of fine sized TiO_2 (Sager *et al.*, 2008). When results were normalized to equivalent surface area, little difference in potency was observed. This was consistent with the two Current Intelligence Bulletins issued by NIOSH for titanium and silver (NIOSH, 2011, 2021). In both instances, the recommended exposure limit, which is a mass-based measurement, for the ultrafine metal compound was less than for the fine sized metal. For titanium, the recommended exposure limit for fine TiO_2 was 2.4 mg/m^3 while ultrafine was 0.3 mg/m^3 (NIOSH, 2011). For silver, the recommended exposure limit for fine silver was 10 $\mu g/m^3$ while ultrafine was 0.9 $\mu g/m^3$ (NIOSH, 2021). These studies clearly indicate that when metals are in the nano size range, health effects are likely to occur at lower exposure levels when measured by mass.

Smoking is a lifestyle choice that has the potential for inhalation exposure to metals. Approximately 75 metals, including cadmium, nickel and chromium, have been detected in cigarettes, and many of these have been identified in smoke (IOM, 2001). More recently, use of electronic cigarettes (e-cigarettes) has become popular. A systematic review of the literature in 2020 found significant metal/metalloid levels (14 different metals discussed) in e-cigarette samples (Zhao *et al.*, 2020). Metals were found in e-liquids, e-cigarette aerosols, and biospecimens of users. It was concluded that the metal/metalloid components of the device generating the aerosol were contributing to metal exposure.

9.20.3.2 Environmental Air Quality and Exposure

Health risks increase for individuals if they have greater exposures or have a greater susceptibility to an exposure. For example, people living in an area near an industrial source may be exposed to higher environmental concentrations than the general population. There can be transport of metals in air from the source, thus increasing the number of people that may be exposed. In the atmosphere, certain metal particles could also undergo a chemical transformation that can result in either a more or less toxic compound. U.S. EPA developed the National-Scale Air Toxics Assessment (NATA) using the 1999 air quality and exposure data (EPA, 1999) and was further updated until 2014 (EPA, 2014). EPA succeeded NATA with the Air Toxics Screening Assessment (EPA AirToxScreen, 2019) from 2017. The most recent AirToxScreen assessment is from 2019. AirToxScreen gives a snapshot of outdoor air quality, and the concentration of various air toxins present in the 50 U.S. states, Puerto Rico, the Virgin Islands, and the District of Columbia. It also includes estimates of cancer and noncancer hazards from these exposures. From the AirToxScreen for most metals, levels of exposure around industrial sites can greatly exceed ambient levels.

9.20.3.3 Occupational Air Quality and Exposure

Occupational exposures are heterogeneous and dependent upon the occupation, workplace (e.g., confined spaces), use of personal protective equipment (if applicable), and the activity of the worker. Most often workers are exposed to specific metals or mixtures at greater concentrations than the general population. Many exposures are mixtures; therefore, elucidating the health outcome from a specific metal is difficult. A worker producing stainless steel alloys would have a different exposure than

Table 1 Resources for environmental and occupational hazards and exposure limits[a]

U.S.A Resources	
https://www.epa.gov	U.S. Environmental Protection Agency
http://www.atsdr.cdc.gov	The Agency for Toxic Substances and Disease Registry
https://www.cdc.gov/niosh	The National Institute for Occupational Safety and Health
https://www.osha.gov	Occupational Safety and Health Administration
https://ntp.niehs.nih.gov	The National Toxicology Program
https://www.acgih.org	The American Conference of Governmental Industrial Hygienists
https://oehha.ca.gov	The Office of Environmental Health Hazard Assessment, California
International Resources	
http://monographs.iarc.fr	International Agency for Research on Cancer, World Health Organization
http://www.av.se	The Swedish Work Environment Authority, Sweden
http://www.hse.gov.uk	Health and Safety Executive, United Kingdom
https://at.dk	The Danish Working Environment Authority, Denmark
https://osha.europa.eu	European Agency for Safety and Health at Work
https://www.kosha.or.kr	Korea Occupational Safety and Health Agency, Korea
https://www.osha.gov.tw	Occupational Safety and Health Administration, Taiwan
https://www.jisha.or.jp	Japan Industrial Safety and Health Association, Japan

[a]This list is not intended to be extensive and all-inclusive but provided to have some initial source of information regarding exposure guidelines, ambient levels, health effects, known source of exposures and exposure limits of environmental and occupational hazards.

a worker soldering with stainless steel. Although these occupational operations are responsible for following OSHA rules, the potential for exposure will still vary. More details on potential exposure from various operations can be found on the OSHA metals website (OSHA).

9.20.3.4 Health-Based Exposure Guidelines and Regulations

Several U.S. agencies (EPA, NIOSH, and OSHA), national and international organizations (e.g., American Conference of Governmental Industrial Hygienists (ACGIH), IARC), and several other countries issue health-based guidelines that typically indicate exposure levels likely to cause noncancer effects and estimated qualitative and quantitative cancer risks. Guidance is routinely updated as new information and methodology becomes available. The interested reader should utilize online sources to obtain the most up-to-date exposure guidelines, paying attention to the specific methodology used and the date of the assessment. **Table 1** provides some organizations that provide guidelines as well as exposure limits in occupational and ambient environment.

9.20.3.5 Mixtures

The contribution of the individual components of a mixture to pulmonary toxicity is a critical research area in toxicology. A wealth of literature exists on single toxicant exposures as opposed to mixtures because dissection of a complex mixture in a controlled setting often proves difficult. Welding, a common industrial process to join metals, is an example of an occupation in which exposure to highly complex mixed metal aerosols occurs. High temperatures ($>4000\ ^{\circ}C$) heat the base metal pieces to be joined and the electrode or wire that is fed into the weld. The generated welding fume is derived primarily from the electrode or wire, which is partially volatilized during the process. The vaporized metals react with air, producing metal oxide particles with an aerodynamic diameter of $< 1\ \mu m$. The fume is considered a process-derived or incidental nanoparticle as significant numbers of ultrafine ($< 0.1\ \mu m$) particles are formed (Antonini, 2003; Guha *et al.*, 2017; IARC, 2018). Mixtures of metals including iron, chromium, manganese, zinc, and nickel among others may be present and, as such, both respiratory and non-respiratory adverse health effects are well-documented in workers. Respiratory effects of welding include metal fume fever, chronic bronchitis, siderosis, lung function decrements, and immunosuppression (Zeidler-Erdely *et al.*, 2012). In 2017, welding fumes were classified by IARC as a Group 1 carcinogen (carcinogenic to humans) (Guha *et al.*, 2017; IARC, 2018).

Workplace exposure limits have aligned with the research on mixtures and regulations are primarily based on the singular, and usually the most hazardous, component. For example, the previous welding fume (not otherwise specified) threshold limit value-time weighted average was retracted in 2004 and emphasis was placed on regulating exposures to the individual metal components (e.g., chromium). This may not be the best practice, however, as questions remain regarding the toxicity of other metals present in welding fumes that have been typically categorized as less toxic or a nuisance, such as iron. The issue of exposure limits remains unresolved, but discussions have centered on whether a set of exposure limits may be necessary to protect workers from welding fumes that contain different metal mixtures such as with mild steel (abundant in iron and manganese) and stainless steel (abundant in iron, chromium, and nickel) fumes (Falcone and Zeidler-Erdely, 2019; Zeidler-Erdely *et al.*, 2019).

Experimental animal studies have examined the lung toxicity and tumor promotion potential of welding fumes and associated individual metal oxides commonly found in the fumes, with a focus on mild steel and stainless-steel fumes (Falcone *et al.*, 2018a, 2017, 2018b). Lung inflammation and cytotoxicity were highest for the complete stainless steel welding fume compared to the

individual metal oxide components (iron > chromium > nickel) at deposited doses representing the welding fume composition. This suggests a possible interactive effect of the metals in combination and is consistent with previous studies that report the metal components or soluble/insoluble fractions to be less toxic than the complete welding fume (Antonini *et al.*, 2004; Zeidler-Erdely *et al.*, 2008).

In vivo data concluded that mild steel and stainless-steel welding fumes exhibited a similar potency to enhance lung tumorigenesis, and iron (as iron (III) oxide; Fe_2O_3) alone acted in the same manner (Falcone *et al.*, 2018a, 2017, 2018b). In a two-stage (initiation-promotion) tumor model, Fe_2O_3, which is a Group 3 agent (not classifiable as to its carcinogenicity to humans) was found to be the primary mediator versus chromium or nickel for the *in vivo* promotion of lung tumors (Falcone *et al.*, 2018b; IARC, 1987). Occupational exposures during iron and steel founding and hematite underground mining are Group 1 carcinogens (IARC, 2012b, c); however, the effects of iron alone, specifically in humans, are difficult to assess as the exposure is nearly always mixed with other metals or potential carcinogens (Bourgkard *et al.*, 2009; IARC, 2012b, c; Siew *et al.*, 2008; Wild *et al.*, 2009). Studies suggest that iron may have carcinogenic effects (IARC, 2010; Siew *et al.*, 2008) and identify iron as an area in need of future research, as reviewed in Zeidler-Erdely *et al.* (2019). Indeed, sub-chronic exposure in a complete lung tumor mouse model indicated that Fe_2O_3 exposure alone may confer carcinogenicity at or near the threshold of significance and that subsequent, even sub-threshold, exposures could result in a carcinogenic effect (Zeidler-Erdely *et al.*, 2020).

Residual Oil Fly Ash (ROFA), an emission source air pollutant from fuel oil combustion, is another heterogeneous metal-rich aerosol exposure. Experimental animal data indicated oxidative stress, inflammatory lung injury, airway hyperreactivity, and increased susceptibility to infection in the lung after ROFA exposure (Ghio Andrew *et al.*, 2002; Roberts *et al.*, 2009). The metal composition of the ash appears critical to the development of airway hyperreactivity (Ghio Andrew *et al.*, 2002; Pritchard *et al.*, 1996). Human health effects may include "boilermakers' bronchitis" or "vanadium bronchitis" in workers. Individuals may also experience sore throat, hoarseness, cough, rhinitis, dyspnea, wheezing, and pneumonitis-like symptoms after high ash concentration exposure. Decreased pulmonary function has also been observed (Ghio Andrew *et al.*, 2002; Hauser *et al.*, 1996, 1995; Sjoberg, 1954; Wyers, 1946). Most of the effects tend to resolve within a few days or weeks of cessation of the exposure (Lees, 1980).

The toxicity of the individual metals in ROFA, typically water-soluble transition metals such as vanadium, nickel, iron, zinc, and copper, remains unclear but are implicated in the health effects associated with ROFA exposure. Deferoxamine, a metal chelator for iron (III) and vanadium (II) but not nickel (II), was not effective in blocking the acute lung injury induced by ROFA (Dockery *et al.*, 1993; Dreher *et al.*, 1996, 1997). Therefore, like welding fumes, there appears to be an interaction among the metals needed to cause an effect. A recent focus in ROFA toxicological research, centers on chemical speciation evaluation of the metal components, namely iron and nickel, to glean knowledge of toxic potential as well as the formation, origin, and fate of the pollutants (Pattanaik *et al.*, 2016).

9.20.4 Deposition and Pulmonary Handling

"The dose makes the poison" is an adage in the field of toxicology. The dose relates specifically to the amount of a given substance that enters the body, usually either by ingestion, injection, absorption, or inhalation. The accumulated or deposited dose then determines the relationship to an adverse event. In terms of respiratory toxicology, several factors influence a pulmonary deposited dose. These include the concentration of an exposure, ventilation rate, and the duration of exposure. The concentration, usually expressed as a mass per unit volume (e.g., mg/m^3), is a representation of the amount of the substance in the air. Exposure limits are often set by a mass concentration. Ventilation rate is the amount of air entering the lung in a unit of time, often expressed as L/min. This value is dependent on such things as physical exertion, anatomy of the respiratory tract, and health status. The duration of exposure is simply how long one is exposed to the substance. This is certainly of importance for occupational setting when the exposure is something specific to the workplace.

The dosimetry of metals in humans is complex. Dosimetry refers to estimating or measuring the amount (e.g., mass, number, surface area, volume) of particles at specific target sites at given times. Thus, dosimetry covers the deposited dose described above, clearance, and retention. Pulmonary deposition includes the processes responsible for removing particles from the airstream, while clearance involves the rates and routes by which deposited particles are removed from the respiratory tract. Retention of metal particles at specific locations within the body reflects the net difference between deposition and clearance processes. The retained dose changes over time as a function of the exposure concentration and the duration of exposure. Gender, age, smoking status, and preexisting disease state can affect the deposition, clearance, and retention of inhaled particles. The information in this section on the various factors involving deposition, retention, and clearance of particles in laboratory animals and in humans is derived primarily from and is also discussed in other publications (Asgharian *et al.*, 2018; Chou *et al.*, 2022; Darquenne, 2012, 2020; EPA, 1996, 2004; Gardner, 2006; Geiser and Kreyling, 2010; Kuempel *et al.*, 2015; Löndahl *et al.*, 2013; McClellan and Henderson, 1995; Méndez *et al.*, 2010; Schlesinger, 1985, 1989).

9.20.4.1 Pulmonary Deposition

The transport of metal particles entrained in inhaled air is governed by laws of physics and is dependent on the physicochemical characteristics of the metal particulate itself. These characteristics include such things as the size, dissolution rate, and chemical

composition. The primary mechanisms for removing particles from the airstream are inertial impaction, sedimentation, and Brownian diffusion. Other factors include interception, electrostatic precipitation, and turbulent flows.

Inertial impaction is the result from sudden change in the direction of flow where the inertia of particle 'impacts' the airway. This mostly occurs in the upper respiratory tract (entrance of the trachea) and upper conducting airways (bifurcations of large airways). This is usually for particles greater than 5 μm. Gravitational sedimentation is the settling of particles under gravity, meaning when the gravitational force begins to exceed the resistive forces of the air. This occurs mostly in the smaller conducting airways as the diameters of the airways begins to get smaller and mostly involves particles ranging from 1–8 μm. Brownian diffusion is the mechanisms of deposition resulting from random motions of particles caused by collisions with gas molecules. This is the primary deposition mechanisms for particles less 0.5 μm and the deposition pattern is in the deepest portion of the lung, the acinus, where gas exchange occurs.

The other mechanisms also play a role in particulate deposition. Interception is an important mechanism for high aspect ratio materials, such as fibers, when one edge of a fiber comes in contact with an airway. With the emergence of engineered nanomaterials, metals can be made into wires and nanobelts capable of reaching the deeper portions of the lung meaning this mechanism of deposition has relevance. Electrostatic precipitation is whether the particles are electrostatically charged. This is not considered a major mechanism for deposition. Turbulent mixing, which is initiated in the upper airways, results from the significant change in diameter of the airways and is propagated into the bronchiolar region. The flow fluctuations resulting from turbulent mixing causes deposition in the airway walls.

9.20.4.2 Regional Respiratory Tract Deposition of Metals

The major determinants of the relative importance of the above deposition mechanisms are the geometric and aerodynamic equivalent particulate diameters. The size, shape, and density of a particle are incorporated into the aerodynamic diameter (d_{ae}), which is defined as the diameter of a unit-density (i.e., 1 g/cm^3) sphere that has the same terminal settling velocity as the particle. Since particles differing in size and density can have the same d_{ae}, they can deposit in the same sites within the respiratory tract. Typically, metals emitted from combustion processes are usually in the fine mode (i.e., $<$ 2.5 μm aerodynamic diameter, d_{ae}), whereas particulate metals from natural sources are usually in the coarse mode (i.e., $>$ 2.5 μm d_{ae}).

Normally, few airborne particles above 15 μm d_{ae} penetrate to the trachea of humans (Miller *et al.*, 1979), with this cut size falling to about 5 μm d_{ae} for laboratory rodents. Since impaction is the major mechanism for head deposition, an impaction parameter incorporating the airflow rate and the d_{ae} is typically used to describe head deposition. Basically, however, head deposition for both adult humans and laboratory animals is slight (i.e., $<$ 15%) for particles $<$ μm d_{ae} and rapidly increases for larger particles. For humans, average peak particle deposition of 40%–50% in the conducting airways is associated with particles about 4–5 μm d_{ae}, with the peak being larger for oronasal compared to that for nasal breathing. In laboratory rodents, deposition is minimal (i.e., only a few percent) in conducting airways over particle sizes ranging from 0.1 to about 5 μm d_{ae}. In humans, there is only a modest deposition of a few percent in the conducting airways for particles $<$ 1μm d_{ae}.

For particles $>$ 1 μm d_{ae}, there is enhanced alveolar deposition when adults breathe through the mouth as compared to the nose; below 1 μm d_{ae}, the two routes of breathing yield similar alveolar deposition efficiencies of about 10–20%, with the minimum for deposition occurring at about 0.5 μm. Typically, about 60–70% of particles between 0.1 and 1 μm do not deposit in the respiratory tract and are exhaled. The peak for alveolar deposition of about 40%–50% occurs at a d_{ae} of about 3.5 μm in adult humans, with deposition falling to only a few percent for 10 μm d_{ae} particles. In laboratory rodents, there is significant variability in deposition for particles between 0.1 and 1 μm d_{ae}, with an average peak deposition of about 30% at 1 μm d_{ae} and a rapid decrease to only a few percent once particle size reaches 4–5 μm d_{ae}.

Deposition of ultrafine particles, which are those particles having a diameter $<$ 0.1 μm, is also of interest because at a given mass there is a relatively large number of particles and particle surface area compared to an aerosol having a larger size. Increased production of engineered nanomaterials within the last decade has led to increased human exposure especially in the occupational setting since they can be taken up via the inhalation route (Dahm *et al.*, 2018; Schubauer-Berigan *et al.*, 2018). To date, human studies have only reported total respiratory tract deposition of ultrafine particles (e.g., (Jaques and Kim, 2000; Löndahl *et al.*, 2007; Schiller *et al.*, 1988)). Total respiratory tract deposition increases from about 30% to 90% as particle size decreases from 0.1 to 0.01 μm. Modeling the deposition to examine the regional deposition of particles, including ultrafine, in the lungs of humans is continually improving (Asgharian and Price, 2007; Chou *et al.*, 2022; Geiser and Kreyling, 2010; Löndahl *et al.*, 2013). A widely used computational model for estimating deposition and clearance for inhaled aerosols is the multiple-path particle dosimetry model (Anjilvel and Asgharian, 1995; Applied Research Associates Inc (ARA), 2023; Miller *et al.*, 2016). This model, which is routinely updated as new data becomes available, is widely accepted internationally, and has deposition/clearance predictions for humans, children (deposition only), and laboratory animals of various species.

9.20.4.3 Pulmonary Handling

Clearance and/or translocation to other sites within the respiratory tract or external to it occur once metal particles have deposited on airway surfaces. The mechanisms that are operative for clearance and translocation differ among the head, conducting airways, and alveolar regions. Mechanical transport of intact particles is involved with most clearance mechanisms, with dissolution being

the only absorptive process. Particles are classified categorically ranging from highly soluble to poorly soluble or insoluble, using data on the rate of dissolution of the particles compared to their rate of clearance by mechanical transport. Dissolution kinetics appears to be a key factor determining the fate of and toxicity of a metals (Kuempel *et al.*, 2015; Smyth and Hickey, 2011; Thomas *et al.*, 2018; Utembe *et al.*, 2015). Indeed, several organizations propose using dissolution as a key parameter in grouping materials for performing read across for hazard assessment (British Standards Institution, 2007; Keller *et al.*, 2021; Kuempel *et al.*, 2012; Lamon *et al.*, 2019).

Poorly soluble particles that deposit on nasal olfactory epithelium can have an extended time for bioavailability. Subsequent uptake by olfactory cells can result in retrograde neuronal transport to the brain, as has been shown for cadmium (Sunderman, 2001) and manganese (Aschner *et al.*, 2005; Santamaria and Sulsky, 2010). Deposited particles that are highly soluble are likely to be rapidly absorbed into epithelial cells independent of the region of deposition. For non-hygroscopic and relatively insoluble metal particles, clearance via the mucociliary escalator occurs for particles deposited in the conducting airways. Some areas within airway bifurcations have regions of non-ciliated cells, leading to prolonged retention in these regions; interestingly, these regions have been shown to be hot spots for particle deposition due to enhanced impaction at these sites during inhalation (Lippmann and Schlesinger, 1984). Another potential mechanism for clearance of particles deposited in conducting airways is through phagocytosis by resident macrophages (Gehr *et al.*, 1991; Geiser *et al.*, 1990).

Clearance of insoluble particles in the alveolar region is typically on the order of months to years (Gardner, 2006). Clearance from the alveolar region can occur through phagocytosis of deposited particles by macrophages located either in the airway lumen or in the interstitium, with eventual removal via either the mucociliary escalator or transfer to the lymphatics. If the particles are small enough (e.g., nanoparticles), they can be taken up by pinocytosis. Particles escaping cellular uptake can pass through the capillary endothelium and directly enter the bloodstream. Which mechanisms and pathways are operative depends upon exposure rate and concentration, particle size, particle number, and current mass loading of particles. While the same pathways for clearance of particles can be found in both laboratory animals and humans, their relative importance can vary considerably among species (Corley *et al.*, 2012; Phalen and Mendez, 2009).

Dissolution of deposited metal particles can be a significant factor in their fate and toxicity. Highly soluble forms (e.g., zinc, copper, silver) are rapidly dissolved in the mucous and surfactant layers that line the respiratory tract. They can then rapidly diffuse into the epithelium and be absorbed into the bloodstream and transported to various extrapulmonary sites (e.g., liver). Less soluble metal particles may be retained in the lung for longer periods of time, potentially producing local effects at the sites of deposition and a variety of chronic lung diseases or may be slowly absorbed into the blood in a "timed-release" fashion. Insoluble particles may ultimately be removed from the lung by various clearance mechanisms (e.g., macrophage phagocytosis, mucociliary clearance).

9.20.5 Inhaled Metal-associated Health Effects

Much is known about the toxicity of inhaled metals, but a lot remains to be learned, especially in terms of mixtures. This section discusses how exposure to a variety of airborne metals results in a well-documented range of pulmonary effects in humans and experimental models. The section is not all inclusive, but an illustration of the potential toxicities that may arise from metal inhalation. In most cases a metal or mixture will be highlighted to illustrate a known mechanism of effect.

9.20.5.1 Risk Factors

Several factors influence the risk paradigm including the exposure, dose, and toxicity of metals. Speciation of the metal itself, health status of the exposed individual, and route of exposure are just some of the risk factors that will contribute to potentially adverse health effects.

9.20.5.1.1 Metal speciation

The chemical form or speciation of the metal is an important factor. It alters the solubility, pulmonary absorption, reactivity, distribution, bioavailability, and ultimately the toxic response (Yokel *et al.*, 2006). Therefore, the toxicity of certain metals (e.g., arsenic, cadmium, chromium, nickel, manganese) is related to their chemical species. Regulatory standards or guidelines typically focus on metal compounds, however. For example, water-soluble nickel compounds (e.g., nickel chloride and sulfates) are more toxic than less-soluble forms, such as nickel oxide. Metals may exist in elemental, ionic, or organic forms, and this also effects the toxicity. Organic arsenic compounds are less toxic than their inorganic forms because they are not as rapidly adsorbed. Alterations in speciation can increase the bioavailability of the metal; for example, methylation of metals generally increases toxicity by making them more lipid-soluble and facilitating their transport across the lipid bilayer (Templeton, 2015). Oxidation or valence state of a metal is an important criterion that determines its bioavailability, persistence, and toxicity. Indeed, it has been used as a predictive paradigm for determining oxidative stress and acute pulmonary inflammation (Zhang *et al.*, 2012). In the environment, chromium predominantly exists in two valence states, each producing different effects. Only the hexavalent form of chromium is considered a carcinogen (ATSDR, 2012b; EPA, 2010, IARC). The trivalent form is considered less toxic because it does not cross biological membranes as efficiently as the hexavalent form. In addition, hexavalent chromium has a higher redox potential, which

enables it to be rapidly reduced to the trivalent form and is involved in oxidative cycling that creates reactive oxygen radical species, which contribute significantly to toxicity. Similarly, ferrous iron (iron (II)) is an essential micronutrient, whereas ferric iron (iron (III)) is toxic. In contrast, some metals elicit similar responses regardless of their form, even though their potency may differ. For example, all forms of cadmium can cause lung inflammation (ATSDR, 2012a).

9.20.5.1.2 Susceptibility factors

Risk factors may increase susceptibility to an adverse health effect from an inhalation exposure including airborne metals. Certain population subsets are more susceptible including children, the elderly, and pregnant individuals. Research now indicates subsequent generations can be impacted after a maternal exposure during pregnancy. Those with preexisting diseases such as asthma and other respiratory diseases, cardiovascular disease, metabolic syndrome, and renal disease are also at an increased risk of an adverse effect following a pulmonary exposure. This risk was illustrated for an adverse cardiovascular event after particulate matter inhalation in susceptible populations (Brook *et al.*, 2010). Some populations, such as children, people who exercise in the presence of airborne metals, or smokers, have slower pulmonary clearance and are likely to receive a higher dose to their respiratory tract. Some individuals or populations may receive a higher exposure, such as those working or living in an unprotected environment or near an exposure source. Genetic differences may influence the metabolism of a metal once it enters the body. For example, alterations in arsenic metabolizing genes have been associated with some arsenic related diseases (Banerjee and Giri, 2015), although references on polymorphisms related to the respiratory track of the metals of interest here could not be found.

9.20.5.1.3 Multiple exposure pathways

Exposure pathways are the relationship between environmental quality and proximate source(s) of exposure. For example, a metal may enter the air and be deposited on the soil or in water, thus entering the food chain. The metal could also be inhaled from the air as part of the original air emission, re-entrainment of deposited material, or a combustion process related to disposal of materials containing the metal. The same metal may directly enter the water supply. Thus, humans could encounter multiple pathways of exposure, ultimately resulting in total dose to target organ(s). Human exposure to metals occurs through all three occupational/environmental routes—oral, dermal, and inhalation. While inhalation is the route of interest for respiratory effects, the lung can also be a target of ingested metals as well.

The route of exposure may be far more important than the intake per route. Sometimes the inhalation route is dismissed because only a relatively small fraction enters the body via this route. The case of cadmium aptly demonstrates the importance of considering routes. For cadmium, the inhalation route is more toxic than the oral route despite greater amounts consumed orally (ATSDR, 2012a; Gerrity and Henry, 1990). Interestingly, arsenic is unique in that it is considered a lung carcinogen when exposures occur through either inhalation or ingestion (Goering *et al.*, 1999; IARC, 1980, 2004). Metals may have different toxicokinetic and toxicological properties via oral and inhalation routes.

9.20.5.2 Mechanisms of Metal-Induced Toxicity and Cell Death

Metal oxides induce toxicity and death at the cellular level through various mechanisms. Some important mechanisms of toxicity and routes of cell death are summarized in this section. Metal ions produced may induce reactive oxygen species (ROS) and apoptosis through direct and indirect interactions (Kodali and Thrall, 2015). Metals induce pro-oxidant effects that causes lipid peroxidation and membrane damage (Schaich, 1992). Some metal ions directly bind to the sulfhydryl groups of biomolecules. Direct interaction with biomolecules, such as metallothionine or glutathione, can reduce the antioxidant pool and promote accumulation of intracellular ROS. Ion interaction with proteins may also lead to accumulation of unfolded or misfolded proteins in the lumen of endoplasmic reticulum and generation of endoplasmic reticulum stress (Rana, 2020). These pathways can cause imbalance in cellular redox status, exacerbating the oxidant production in the cells. There may also be direct interaction with mitochondrial membrane proteins causing mitochondrial membrane permeability. Intracellular ROS generated by metals can also be exacerbated by the mitochondria. With either route, mitochondrial membrane damage causes release of cytochrome c and activation of a potent caspase activation pathway leading to apoptosis (Garrido *et al.*, 2006). Metal ions can also cause direct damage to DNA and in some cases metals like cadmium and magnesium produce ions that can weaken binding of p53 to DNA, which causes DNA damage and apoptosis. Metal ions can also modulate cell survival genes through DNA methylation and histone post-translational modifications (Salnikow and Zhitkovich, 2008).

Several metals and metalloids including zinc and silica cause lysosomal membrane damage and promote ROS production leading to activation of NLRP3 inflammasome (Huang *et al.*, 2023). Inflammasome activation leads to strong inflammatory response, caspase-1 release, and "pyroptosis", a regulated inflammatory cell death. Iron is an essential metal that plays an important role in the cellular metabolism and function. Excess iron in the cells produces ROS by the Fenton reaction, impaired antioxidant production, and mitochondrial dysfunction. These excess oxidants then react with the polyunsaturated fatty acid (PUFA)-containing phospholipids causing ultimately cell death. This distinctive iron-dependent form of cell death is referred to as ferroptosis. Apart from iron, exposure to several metals including arsenic, cobalt, cadmium, iron, magnesium, manganese, nickel, mercury and zinc (Sahoo and Sharma, 2023) are also known to cause dysbiosis in cellular iron homeostasis, leading to ferroptosis.

Trace amounts of copper is essential for proper functioning of several enzymes. Intracellular copper is low at homeostatic condition. Excess buildup of copper can lead to its binding to lipoylated enzymes in the tricarboxylic acid cycle, leading to protein aggregation, proteotoxic stress, and ultimately cell death. This mode of cell death due to excessive copper is termed cuproptosis (Tang *et al.*, 2022). The hallmark of cuproptosis is the aggregation of lipoylated proteins using copper ion as a core.

9.20.5.3 Immune Regulation by Metals

Exposure to metals is known to induce several innate and adaptive immune effects including immunosuppression, immune stimulation, contact dermatitis (ACD), asthma, allergic sensitization, and adjuvancy. This section discusses some of the pulmonary immune effects due to metal exposure.

The respiratory system is composed of specialized tissues and cells with important functions apart from those related to respiration. The lung immune system is composed of nonspecific (natural immunity) and acquired components. The pulmonary immune system is a sensitive target for toxicity from many inhaled metals. A wide range of airborne metals have the capability to interact with the immune system. The immunocompetence status of the exposed subject is an important factor in susceptibility. Exposure to airborne metals can depress a variety of host defense mechanisms, including mucociliary clearance in the airways, pulmonary macrophage function, and the development of specific immune responses (e.g., IgG antibody production and cell-mediated immunity). Consequences can range from an increased incidence of infections to possible tumor cell growth.

Of particular importance in pulmonary innate immune responses is the airway epithelium. The airway epithelium is the first line of defense from inhaled particulates, pathogens, allergens, and toxicants (Vareille *et al.*, 2011). In addition to providing a physical barrier, the airway epithelium coordinates innate immune defense by responding to inhaled insults with a dynamic range of cellular mediators. Along with the epithelium, the dense basement membrane (BM) is essential for proper epithelial function. The BM anchors the epithelium, establishes and maintains epithelial polarity, provides survival signals to the epithelium, and acts as a barrier between the epithelium and the underlying mesenchyme. Because of the exposure to pollutants and infectious agents, the epithelium is constantly undergoing cellular renewal. If there is an injury to the epithelium, wound repair mechanisms are initiated to reestablish the epithelial barrier which can be altered by metal exposure. Airway epithelial cells from animals exposed to arsenic through inhalation have a decreased ability to repair damage, to establish tight junctions between cells, and restore epithelial function (Sherwood *et al.*, 2012). This decreased ability to repair damaged epithelium predisposes the lung to increased infections, increased airway hyperreactivity, and increased alterations in extracellular matrix leading to decreased lung function and obstructive/restrictive lung disease.

The immunosuppression caused by metals may be local, affecting specific cells within the lung, or may be generalized, producing systemic effects. Such impairment of immunocompetence can represent a significant hazard to human health. Exposure by inhalation to arsenic, nickel, cadmium, and mercury can lead to such effects as well as metal mixtures such as welding fume. This can lead to increased infection risk of individuals exposed to metals (Zeidler-Erdely *et al.*, 2012). Exposure to metals impairs resistance to bacterial and viral infections in animals (Gilmour and Gowdy, 2006). The mechanisms of action are often attributed to redox imbalance and alteration in innate immune pulmonary host defenses. For example, effects include a decrease in phagocytic function and reduced bactericidal activity, macrophage numbers, and viability (Gardner, 1984; Kodali *et al.*, 2013).

In addition, immune stimulation in the form of increased T-cell activity and IgE antibody formation can cause hypersensitivity reactions (e.g., pneumonitis, allergic responses, occupational asthma, and bronchitis). Such reactions may also result in autoimmune disease, which encompasses a variety of immunopathological states and can affect most organ systems. Sometimes inhaled chemicals may cause more than one type of immune response, depending on the specific chemical and the concentration and duration of exposure.

Inhalation of some metals may result in respiratory allergic disease. Epidemiological studies correlated metals in air pollution to asthma (Godri Pollitt *et al.*, 2016; Kusaka *et al.*, 1996; Wu *et al.*, 2019). Allergic disease is a complex chronic inflammatory response of the airways. Its etiology is multifactorial, involving the recruitment and activation of many inflammatory and structural cells, all of which release inflammatory mediators that result in pathological changes. Allergies are classified as hypersensitivity diseases and may be immediate or delayed, based on the development of the response (Sarlo and Baccam, 2007).

Hypersensitivity reactions to inhaled nickel have been reported in mining and refining, alloy production, and waste incineration (Gardner, 2006). Workers with a positive skin test have a higher incidence of immediate (Type I) reactions, possibly resulting in edema and bronchial obstruction. This response is a result of the release of bioactive amines from mast cell granules stimulated by cross-linking of surface immunoglobulin E (IgE) by the inhaled antigen. Other metals of relevance to this article, namely chromium, are thought to cause immediate hypersensitivity reactions following inhalation. Upon re-exposure to the allergen, there is a release of vasoactive amines and other mediators from mast cell degranulation, resulting in inflammation and bronchoconstriction. Hypersensitivity pneumonitis from mercury is an example of a combined Type III and IV hypersensitivity reaction after 4–6 h of exposures to the sensitizing agent.

Metals also can modulate allergic responses to nonmetal allergens. Aluminum hydroxide is widely used as a vaccine adjuvant and is known to activate pattern recognition receptors, induce Th2 response and improve uptake by antigen presenting cells. Metals like gold, nickel, and cobalt induce pro-inflammatory signaling by directly interacting with the receptors (Rachmawati *et al.*, 2013; Schmidt and Goebeler, 2015; Schmidt *et al.*, 2010) and promote sensitization by activating dendritic cell (DC) activation. Metals including beryllium and several noble metals modulate communication between innate and adaptive immune cells by inducing alteration in major histocompatibility complex (MHC) impacting interaction with T cell receptor (De Wall *et al.*, 2006; Falta *et al.*, 2013). Metals like nickel are also known to cause peptide-independent linking of MHC and TCR (Gamerdinger *et al.*, 2003; Thierse *et al.*, 2005).

9.20.5.4 Respiratory Pathophysiological Effects

Most information on the effects of human inhalation exposure to metals is derived from occupational settings where the predominant exposure is from metals in airborne dust. The interpretation of worker studies is complicated because of the possibility of exposure to other contaminants in the working environment, including various gases and other heavy metal contaminants, which may also play a role in causing similar responses. In addition, inhaled metals are often associated with particulate matter which by itself can cause pulmonary pathological effects. Separation of the effects of particulate matter (PM) from those of PM associated metals is difficult. Workers often complain of irritation of the nose and throat, which may lead to laryngitis, bronchitis, or rhinitis. It is not always known whether respiratory effects following the inhalation of metals are a direct effect of the specific metal on respiratory tissues, the general effects of having a foreign material in the lungs, or an effect of the metal on the pulmonary vasculature, possibly resulting in inflammation. At high concentrations, acute pulmonary edema and bronchitis may occur. Longer exposures to high levels may lead to emphysema. Long-term exposure to certain metals can result in high retention in lung tissue, leading to pneumoconiosis with obstructive lung disease. The primary non-cancerous health effects including inflammation, pneumoconiosis, bronchitis, emphysema, chronic obstructive pulmonary disease, pneumonitis, asthma, metal fume fever, etc. are indicated in the opening section of this chapter discussing the metals individually. Also included is the potential for systemic effects on the cardiovascular, renal, hepatic, immune, neurological, blood, ocular, endocrine, reproductive, and musculoskeletal systems following an inhalation metal exposure.

9.20.5.5 Carcinogenesis

Three US agencies, the NTP, NIOSH, and EPA, and one international agency, IARC have cancer classification systems for carcinogens. This section will focus on the EPA and IARC classification systems and the respective websites should be consulted for more comprehensive information (EPA IRIS, 2023; IARC). In brief, the EPA first carcinogen risk assessment guidelines, published in 1986, were revised in 2005 to be more comprehensive and transparent for certain topics (e.g., children's risk assessment). The 2005 guidelines are based on a "weight-of-evidence" narrative, versus the previous hierarchical approach, that includes evidence (human, experimental animal, and supporting data), uncertainties, and key assumptions and are expressed separately for oral and inhalation routes. There are five categories: Carcinogenic to Humans, Likely to be Carcinogenic to Humans, Suggestive Evidence of Carcinogenic Potential, Inadequate Information to Assess Carcinogenic Potential, and Not Likely to be Carcinogenic to Humans. Not all agents were reclassified by the EPA and, therefore, maintain the 1986 classification designation (Group A: carcinogenic to humans, B1 and B2: probably carcinogenic to humans, C: possibly carcinogenic to humans, D: not classifiable as to human carcinogenicity, E: evidence of non-carcinogenicity for humans) (EPA, 2005).

The IARC, part of the World Health Organization (WHO), develops highly regarded Monographs on the Identification of Carcinogenic Hazards to Humans (http://monographs.iarc.fr). The Preamble to the IARC Monographs, recently updated in 2019, states the objective and scope of the program, the scientific principles and procedures used in developing a Monograph, the types of evidence considered, and the scientific criteria that guide the evaluations. The process for development of the Monographs has evolved over several decades and continues to do so (IARC, 2019b). As stated in the Preamble, the process "involves the engagement of international, interdisciplinary Working Groups of expert scientists, the transparent synthesis of different streams of evidence (exposure characterization, cancer in humans, cancer in experimental animals, and mechanisms of carcinogenesis), and the integration of these streams of evidence into an overall evaluation and classification according to criteria developed and refined by IARC." There are four categories: carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), and not classifiable as to its carcinogenicity to humans (Group 3).

It is estimated that between 2–8 % of all cancers worldwide are caused by exposures to carcinogens in the workplace and that lung cancer contributes to approximately 28.8% of all fatal occupational diseases (Olsson and Kromhout, 2021; Purdue *et al.*, 2015; Spyratos *et al.*, 2013). IARC has classified several metals, largely associated with workplace exposures, as Group 1 carcinogens for lung such as arsenic, nickel, cadmium, chromium, and beryllium (IARC, 1990, 1993, 2012a). Every five years an international, Interdisciplinary Advisory Group recommends agents (i.e., chemical, physical, or biological entity or exposure circumstance) for review by the Monographs program. Cobalt and antimony compounds were listed as high and medium priority, respectively, by the Advisory Group on the Monograph priorities for 2020–2024 for further evaluation and were evaluated in 2022 (IARC, 2019a; Marques *et al.*, 2019). Other agents of relevance to this chapter, such as welding fumes and indium tin oxide, were evaluated in 2017 (IARC, 2018). Carcinogenic classifications, if available, are listed for each metal in the previous summary section.

For cancer hazard identification, IARC has compiled ten key characteristics (KCs) that carcinogenic agents commonly exhibit. These mechanism-based KCs may aid classification to a different group (e.g., Group 2B to 2A) in cases where epidemiological or animal evidence is limited or even non-existent. The agent may display one or more of these KCs and include characteristics such as 'is genotoxic,' 'is immunosuppressive,' 'induces epigenetic alterations,' or 'induces chronic inflammation.' (Smith *et al.*, 2016). Cobalt metal and trivalent antimony, for example, both exhibit several of the KCs and caused genotoxicity, oxidative stress, chronic inflammation, and alterations in cell proliferation and death *in vitro* and in experimental systems and were recently classified as Group 2A agents (IARC, 2022; Karagas *et al.*, 2022).

Mild steel welding, predominantly an iron exposure, was previously believed to pose little risk for lung cancer development because of the absence of carcinogenic metals, such as chromium and nickel, in the generated fume. However, an increased risk of lung cancer was observed regardless of the welding process/method or material/consumable used, and there was no evidence that the increased cancer risk was limited to exposure to chromium- and nickel-containing stainless steel welding fumes (Langård, 1994; Moulin, 1997; Sørensen *et al.*, 2007). Indeed, experimental animal studies support these epidemiological findings and, more recently, have begun to elucidate the potential role of iron in welding fume-induced lung cancer (Falcone *et al.*, 2018a, 2018b; Zeidler-Erdely *et al.*, 2020). The mechanisms by which welding fumes act as lung carcinogens remain largely unknown; however, the most likely KCs include the ability to cause immunosuppression and chronic inflammation (Guyton *et al.*, 2018). Welding fumes cause sustained cellular influx in experimental animal models and epidemiology studies indicate that welders and metal fume workers are more susceptible to develop an infection (Coggon *et al.*, 1994; David and Keith, 2016; Palmer *et al.*, 2003). In agreement, welding fumes and its component surrogate metal oxides induced an immunosuppressive state in the rodent lung (Antonini and Roberts, 2007; Antonini *et al.*, 2009; Falcone *et al.*, 2018b); Increased DNA damage has also been reported in blood leukocytes from welders exposed to chromium- and nickel-containing welding fumes as well as in *in vitro* systems (Costa *et al.*, 1993; Danadevi *et al.*, 2004; Leonard *et al.*, 2010).

Hexavalent chromium is known to cause lung cancer and other types of cancer in human (IARC, 1990). Inhaled hexavalent chromium particles are retained primarily by the lung and tend to accumulate near major bifurcations, where they may persist for many years (Ishikawa *et al.*, 1994a, 1994b). Hexavalent chromium undergoes a series of metabolic reductions inside cells to generate reactive species; therefore, KCs of focus in previous studies largely include genotoxicity and oxidative stress (Zhu and Costa, 2020). Epigenetic effects (i.e., DNA or histone modifications), and even more recently "epi-transcriptomics" or biological effects of RNA modifications, have begun to emerge as important mechanisms of carcinogenesis for chromium as well as other metals (Chen, 2019; Saletore *et al.*, 2012; Wang *et al.*, 2022; Yang and Wang, 2022; Zhu and Costa, 2020)

The carcinogenic metals, arsenic and cadmium have been shown to suppress cell autophagy *in vitro*. Autophagy plays an important role in tumor suppression; therefore, this may be another relevant emerging mechanism of metal-induced carcinogenicity (Codogno and Meijer, 2005; Kimura *et al.*, 2016; Liu *et al.*, 2017). Arsenic-induced carcinogenesis may also involve alterations in DNA methylation, histone modifications, inhibition of DNA repair, and oxidative stress (Chen *et al.*, 2019; Zhu and Costa, 2020). It is apparent that the carcinogenic activity of a metal is likely not due to a singular mechanism. It is imperative that future research, particularly with mixed metal exposures like welding, be utilized to decipher additional additive or synergistic mechanisms involved.

9.20.6 Summary

- Metal inhalation mostly results in an adverse health effect. Some effects are acute and resolve, while prolonged exposure may result in pathology and cancer.
- Higher exposures tend to occur in occupational settings rather than in ambient environment for most metals.
- Metal exposure can result in deposition in all lung regions. The development of nanoscale metals, or metals with a size that easily reach the deeper regions, increased the potency of effect due to increased surface area/reactivity per unit mass.
- Health effects vary by the metal itself, the speciation of a specific metal, physicochemical characteristics, susceptibility of an individual, and exposure / deposited pulmonary dose.
- Dependent on the metal and its physico-chemical property, health effects after inhalation have a wide range of outcomes within the lung and also in systemic organ systems.

Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Mention of brand name does not constitute product endorsement.

References

Anjilvel, S., Asgharian, B., 1995. A multiple-path model of particle deposition in the rat lung. Fundamental and Applied Toxicology 28, 41–50.
Antonini, J.M., 2003. Health effects of welding. Critical Reviews in Toxicology 33, 61–103.
Antonini, J.M., Roberts, J.R., 2007. Chromium in stainless steel welding fume suppresses lung defense responses against bacterial infection in rats. Journal of Immunotoxicology 4, 117–127.
Antonini, J.M., Roberts, J.R., Stone, S., *et al*., 2009. Short-term inhalation exposure to mild steel welding fume had no effect on lung inflammation and injury but did alter defense responses to bacteria in rats. Inhalation Toxicology 21, 182–192.
Antonini, J.M., Taylor, M.D., Zimmer, A.T., Roberts, J.R., 2004. Pulmonary responses to welding fumes: Role of metal constituents. Journal of Toxicology and Environmental Health, Part A 67, 233–249.
Applied Research Associates Inc (ARA), 2023. Multiple-Path Particle Dosimetry Model (MPPD v 3.04) [Online]. Available: https://www.ara.com/mppd/ (Accessed 09/10 2023).
Aquino, N.B., Sevigny, M.B., Sabangan, J., Louie, M.C., 2012. The role of cadmium and nickel in estrogen receptor signaling and breast cancer: Metalloestrogens or not? Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews 30, 189–224.
Aschner, M., Erikson, K.M., Dorman, D.C., 2005. Manganese dosimetry: Species differences and implications for neurotoxicity. Critical Reviews in Toxicology 35, 1–32.
Asgharian, B., Owen, T.P., Kuempel, E.D., Jarabek, A.M., 2018. Dosimetry of inhaled elongate mineral particles in the respiratory tract: The impact of shape factor. Toxicology and Applied Pharmacology 361, 27–35.
Asgharian, B., Price, O.T., 2007. Deposition of ultrafine (nano) particles in the human lung. Inhalation Toxicology 19, 1045–1054.
ATSDR, 2012a. Toxicological profile for cadmium. Public Health Service, Centres for Diseases Control. Atlanta, GA: US Department of Health and Humans Services.
ATSDR, 2012b. Toxicological profile for chromium. US Department of Health and Human Services. Public Health Service.
ATSDR Tox Profiles, 2023. Toxicological Profiles (Tox Profiles) [Online]. Department of Health and Human Services, Public Health Service. Available: https://www.atsdr.cdc.gov/toxprofiledocs/index.html (Accessed 09/06 2023).
ATSDR ToxGuides, 2023. ToxGuides [Online]. Department of Health and Human Services, Public Health Service. Available: https://wwwn.cdc.gov/TSP/ToxGuides/ToxGuidesLanding.aspx (Accessed 09/06 2023).
Auffan, M., Rose, J., Bottero, J.-Y., *et al*., 2009. Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective. Nature Nanotechnology 4, 634–641.
Bachmann, J., Damberg, R., Caldwell, J., Edwards, C., Koman, P., 1996. Review of the national ambient air quality standards for particulate matter: Policy assessment of scientific and technical information. OAQPS staff paper. Final report. Environmental Protection Agency, Research Triangle Park, NC (United States ….
Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M.R., Sadeghi, M., 2021. Toxic mechanisms of five heavy metals: Mercury, lead, chromium, cadmium, and arsenic. Frontiers in Pharmacology 12.
Banerjee, M., Giri, A.K., 2015. Genetic epidemiology of susceptibility to arsenic-induced diseases. Arsenic: Exposure Sources, Health Risks, and Mechanisms of Toxicity.
Bourgkard, E., Wild, P., Courcot, B., *et al*., 2009. Lung cancer mortality and iron oxide exposure in a French steel-producing factory. Occupational and Environmental Medicine 66, 175.
British Standards Institution, 2007. Nanotechnologies – Part 2: Guide to safe handling and disposal of manufactured nanomaterials (No. 71.100.99), British Standards Institution.
Brook, R.D., Rajagopalan, S., Pope 3rd, C.A., *et al*., 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121, 2331–2378.
Brugge, D., Buchner, V., 2011. Health Effects of Uranium: New Research Findings 26, 231–249.
Campbell, A., 2002. The potential role of aluminium in Alzheimer's disease. Nephrology Dialysis Transplantation 17, 17–20.
Chen, Q.Y., Murphy, A., Sun, H., Costa, M., 2019. Molecular and epigenetic mechanisms of Cr(VI)-induced carcinogenesis. Toxicology and Applied Pharmacology 377, 114636.
Chen, R., Cheng, J., Lv, J., Wu, L., Wu, J., 2017. Comparison of chemical compositions in air particulate matter during summer and winter in Beijing, China. Environmental Geochemistry and Health 39, 913–921.
Chen, S.J., 2019. Site-specific binding of non-site-specific ions. Biophysical Journal 116, 2237–2239.
Chou, W.-C., Cheng, Y.-H., Riviere, J.E., *et al*., 2022. Development of a multi-route physiologically based pharmacokinetic (PBPK) model for nanomaterials: A comparison between a traditional versus a new route-specific approach using gold nanoparticles in rats. Particle and Fibre Toxicology 19, 47.
Codogno, P., Meijer, A.J., 2005. Autophagy and signaling: Their role in cell survival and cell death. Cell Death & Differentiation 12, 1509–1518.
Coggon, D., Inskip, H., Winter, P., Pannett, B., 1994. Lobar pneumonia: An occupational disease in welders. The Lancet 344, 41–43.
Corley, R.A., Kabilan, S., Kuprat, A.P., *et al*., 2012. Comparative computational modeling of airflows and vapor dosimetry in the respiratory tracts of Rat, Monkey, and Human. Toxicological Sciences 128, 500–516.
Costa, M., Zhitkovich, A., Toniolo, P., 1993. DNA-protein cross-links in welders: Molecular implications. Cancer Research 53 (3), 460.
Csavina, J., Field, J., Taylor, M.P., *et al*., 2012. A review on the importance of metals and metalloids in atmospheric dust and aerosol from mining operations. Science of The Total Environment 433, 58–73.
Csavina, J., Landázuri, A., Wonaschütz, A., *et al*., 2011. Metal and metalloid contaminants in atmospheric aerosols from mining operations. Water, Air, & Soil Pollution 221, 145–157.
Csavina, J., Taylor, M.P., Félix, O., *et al*., 2014. Size-resolved dust and aerosol contaminants associated with copper and lead smelting emissions: Implications for emission management and human health. Science of The Total Environment 493, 750–756.
Cummings, K.J., Nakano, M., Omae, K., *et al*., 2012. Indium lung disease. Chest 141, 1512–1521.
Dahm, M.M., Schubauer-Berigan, M.K., Evans, D.E., *et al*., 2018. Exposure assessments for a cross-sectional epidemiologic study of US carbon nanotube and nanofiber workers. International Journal of Hygiene and Environmental Health 221, 429–440.
Danadevi, K., Rozati, R., Banu, B.S., Grover, P., 2004. Genotoxic evaluation of welders occupationally exposed to chromium and nickel using the Comet and micronucleus assays. Mutagenesis 19, 35–41.
Darquenne, C., 2012. Aerosol deposition in health and disease. Journal of Aerosol Medicine and Pulmonary Drug Delivery 25, 140–147.
Darquenne, C., 2020. Deposition mechanisms. Journal of Aerosol Medicine and Pulmonary Drug Delivery 33, 181–185.
David, C., Keith, T.P., 2016. Are welders more at risk of respiratory infections? Thorax 71, 581.
De Wall, S.L., Painter, C., Stone, J.D., *et al*., 2006. Noble metals strip peptides from class II MHC proteins. Nature Chemical Biology 2, 197–201.
Dockery, D.W., Pope, C.A., Xu, X., *et al*., 1993. An association between air pollution and mortality in six U.S. cities. New England Journal of Medicine 329, 1753–1759.
Doherty, M.J., Healy, M., Richardson, S.G., Fisher, N.C., 2004. Total body iron overload in welder's siderosis. Occupational and Environmental Medicine 61, 82.
Drake, P.L., Hazelwood, K.J., 2005. Exposure-related health effects of silver and silver compounds: A review. Annals of Occupational Hygiene 49, 575–585.
Dreher, K., Jaskot, R., Kodavanti, U., *et al*., 1996. Soluble transition metals mediate the acute pulmonary injury and airway hyperreactivity induced by residual oil fly ash articles. CHEST, 109, 33S–34S.
Dreher, K., Jaskot, R.H., Lehmann, J.R., *et al*., 1997. Soluble transition metals mediate residual oil fly ash induced acute lung injury. Journal of Toxicology and Environmental Health Part A 50, 285–305.

Egorova, K.S., Ananikov, V.P., 2017. Toxicity of metal compounds: Knowledge and myths. Organometallics 36, 4071–4090.
EPA, 1996. Air Quality Criteria for Particulate Matter (Volume II). Research Triangle Park, NC, US Environmental Protection Agency.
EPA, 1999. 1999 National-Scale Air Toxics Assessment [Online]. United States Environmental Protection Agency. Available: https://archive.epa.gov/airtoxics/nata1999/web/html/ (Accessed 09/08 2023).
EPA, 2004. Air Quality Criteria for Particulate Matter, (Vol. 1 &Vol. 2). Research Triangle Park, NC, US Environmental Protection Agency: United States Environmental Protection Agency.
EPA, 2005. Risk Assessment for Carcinogenic Effects [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/fera/risk-assessment-carcinogenic-effects (Accessed 09/08 2023).
EPA, 2006. Provisional Peer Reviewed Toxicity Values for Iron and Compounds. US EPA, Superfund Health Risk Technical Support Center, National Center for ….
EPA, 2010. IRIS Toxicological Review of Hexavalent Chromium. US Environmental Protection Agency Washington.
EPA, 2014. National Air Toxics Assessment (NATA) [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/national-air-toxics-assessment (Accessed 09/08 2023).
EPA AirToxScreen, 2019. Air Toxics Screening Assessment (AirToxScreen) [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/AirToxScreen (Accessed 09/08 2023).
EPA Fact Sheets, 2023. Health Effects Fact Sheets [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/haps/about-health-effects-fact-sheets (Accessed 09/06 2023).
EPA HAP, 2023. Hazardous Air Pollutants [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/haps (Accessed 09/06 2023).
EPA IRIS, 2023. Integrated Risk Information System (IRIS) [Online]. United States Environmental Protection Agency. Available: https://www.epa.gov/iris (Accessed 09/06 2023).
Eto, K., 2000. Minamata disease. Neuropathology 20, 14–19.
EU-OSHA, 2023. European Agency for Safety and Health at Work [Online]. Available: https://osha.europa.eu/en (Accessed 09/06 2023).
Falcone, L.M., Erdely, A., Kodali, V., *et al*., 2018a. Inhalation of iron-abundant gas metal arc welding-mild steel fume promotes lung tumors in mice. Toxicology 409, 24–32.
Falcone, L.M., Erdely, A., Meighan, T.G., *et al*., 2017. Inhalation of gas metal arc–stainless steel welding fume promotes lung tumorigenesis in A/J mice. Archives of Toxicology 91, 2953–2962.
Falcone, L.M., Erdely, A., Salmen, R., *et al*., 2018b. Pulmonary toxicity and lung tumorigenic potential of surrogate metal oxides in gas metal arc welding–stainless steel fume: Iron as a primary mediator versus chromium and nickel. PLOS ONE 13, e0209413.
Falcone, L.M., Zeidler-Erdely, P.C., 2019. Skin cancer and welding. Clinical and Experimental Dermatology 44, 130–134.
Falta, M.T., Pinilla, C., Mack, D.G., *et al*., 2013. Identification of beryllium-dependent peptides recognized by CD4 + T cells in chronic beryllium disease. Journal of Experimental Medicine 210, 1403–1418.
Gamerdinger, K., Moulon, C., Karp, D.R., *et al*., 2003. A new type of metal recognition by human T cells: Contact residues for peptide-independent bridging of T cell receptor and major histocompatibility complex by nickel. The Journal of Experimental Medicine 197, 1345–1353.
Gardner, D.E., 1984. Alterations in macrophage functions by environmental chemicals. Environmental Health Perspectives 55, 343–358.
Gardner, D.E., 2006. Toxicology of the Lung. CRC Press, Taylor & Francis.
Garrido, C., Galluzzi, L., Brunet, M., *et al*., 2006. Mechanisms of cytochrome c release from mitochondria. Cell Death & Differentiation 13, 1423–1433.
Gehr, P., Hof, V.I., Geiser, M., SchÜRch, S., 1991. The fate of particles deposited in the intrapulmonary conducting airways. Journal of Aerosol Medicine 4, 349–361.
Geiser, M., Cruz-Orive, L.M., Hof, V.I., Gehr, P., 1990. Assessment of particle retention and clearance in the intrapulmonary conducting airways of hamster lungs with the fractionator 1. Journal of Microscopy 160, 75–88.
Geiser, M., Kreyling, W.G., 2010. Deposition and biokinetics of inhaled nanoparticles. Particle and Fibre Toxicology 7, 2.
Gerrity, T.R., Henry, C.J. (Eds.), 1990. Principles of route to route extrapolation for risk assessment: In: Proceedings of the workshop held in South Carolina and North Carolina, New York, NY: Elsevier.
Ghio Andrew, J., Silbajoris, R., Carson Johnny, L., Samet James, M., 2002. Biologic effects of oil fly ash. Environmental Health Perspectives 110, 89–94.
Gilmour, M.I., Gowdy, K., 2006. Host defense and immunotoxicology of the lung. In: Robert, V., House, R.L., Ian, K. (Eds.), Immunotoxicology and Immunopharmacology. CRC Press.
Godri Pollitt, K.J., Maikawa, C.L., Wheeler, A.J., *et al*., 2016. Trace metal exposure is associated with increased exhaled nitric oxide in asthmatic children. Environmental Health 15, 94.
Goering, P.L., Aposhian, H.V., Mass, M.J., *et al*., 1999. The enigma of arsenic carcinogenesis: Role of metabolism. Toxicological Sciences 49, 5–14.
Gonzales, P., Felix, O., Alexander, C., *et al*., 2014. Laboratory dust generation and size-dependent characterization of metal and metalloid-contaminated mine tailings deposits. Journal of Hazardous Materials 280, 619–626.
Guha, N., Loomis, D., Guyton, K.Z., *et al*., 2017. Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. The Lancet Oncology 18, 581–582.
Guyton, K.Z., Rusyn, I., Chiu, W.A., *et al*., 2018. Application of the key characteristics of carcinogens in cancer hazard identification. Carcinogenesis 39, 614–622.
Hauser, R., Daskalakis, C., Christiani, D.C., 1996. A regression approach to the analysis of serial peak flow among fuel oil ash exposed workers. American Journal of Respiratory and Critical Care Medicine 154, 974–980.
Hauser, R., Elreedy, S., Hoppin, J.A., Christiani, D.C., 1995. Airway obstruction in boilermakers exposed to fuel oil ash. A prospective investigation. American Journal of Respiratory and Critical Care Medicine 152, 1478–1484.
Huang, W., Zhang, Z., Qiu, Y., *et al*., 2023. NLRP3 inflammasome activation in response to metals. Frontiers in Immunology 14, 1055788.
IARC, 1980. Arsenic and arsenic compounds, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 1987. Overall evaluations of carcinogenicity: An updating of IARC Monographs volumes 1 to 42, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 1990. Chromium, nickel and welding. IARC monographs on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 1993. Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing IndustryBeryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2004. Some drinking-water disinfectants and contaminants, including arsenic.
IARC, 2010. Identification of Research Needs to Resolve the Carcinogenicity of High-Priority IARC Carcinogens, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2012a. Arsenic, metals, fibres, and dusts, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2012b. Chemical Agents and Related Occupations, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2012c. Radiation, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2018. Welding, Molybdenum Trioxide, and Indium Tin Oxide, Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2019a. Report of the Advisory Group to Recommend Priorities for the IARC Monographs during 2020–2024. In: NEWTON, R. (Ed.). International Agency for Research on Cancer, World Health Organization, United Nations.
IARC, 2022. Cobalt, antimony compounds, and weapons-grade tungsten alloy., Lyon, France, International Agency for Research on Cancer, World Health Organization, United Nations.

IARC, 2023. Agents Classified by the IARC Monographs [Online]. Lyon, France: International Agency for Research on Cancer, World Health Organization, United Nations. Available: https://monographs.iarc.who.int/agents-classified-by-the-iarc/ (Accessed 06/09 2023).
IARC, 2019b. IARC Monographs Preamble – Preamble to the IARC Monographs [Online]. Lyon, France: International Agency for Research on Cancer, World Health Organization, United Nations. Available: https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs (Accessed).
IOM, 2001. Clearing the smoke: Assessing the science base for tobacco harm reduction. In: Stratton, K., Shetty, P., Wallace, R., Bondurant, S. (Eds.), Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction. Washington (DC): National Academies Press (US).
Ishikawa, Y., Nakagawa, K., Satoh, Y., *et al*., 1994a. Characteristics of chromate workers' cancers, chromium lung deposition and precancerous bronchial lesions: An autopsy study. British Journal of Cancer 70, 160–166.
Ishikawa, Y., Nakagawa, K., Satoh, Y., *et al*., 1994b. "Hot Spots" of chromium accumulation at bifurcations of chromate workers' Bronchi1. Cancer Research 54, 2342–2346.
Jaques, P.A., Kim, C.S., 2000. Measurement of total lung deposition of inhaled ultrafine particles in healthy men and women. Inhalation Toxicology 12, 715–731.
Karagas, M.R., Wang, A., Dorman, D.C., *et al*., 2022. Carcinogenicity of cobalt, antimony compounds, and weapons-grade tungsten alloy. The Lancet Oncology 23, 577–578.
Keller, J.G., Persson, M., Müller, P., *et al*., 2021. Variation in dissolution behavior among different nanoforms and its implication for grouping approaches in inhalation toxicity. NanoImpact 23, 100341.
Kimura, A., Ishida, Y., Nosaka, M., *et al*., 2016. Exaggerated arsenic nephrotoxicity in female mice through estrogen-dependent impairments in the autophagic flux. Toxicology 339, 9–18.
Kodali, V., Littke, M.H., Tilton, S.C., *et al*., 2013. Dysregulation of macrophage activation profiles by engineered nanoparticles. ACS Nano 7, 6997–7010.
Kodali, V., Thrall, B.D., 2015. Oxidative stress and nanomaterial-cellular interactions. Studies on Experimental Toxicology and Pharmacology. 347–367.
Kuempel, E.D., Castranova, V., Geraci, C.L., Schulte, P.A., 2012. Development of risk-based nanomaterial groups for occupational exposure control. Journal of Nanoparticle Research 14, 1029.
Kuempel, E.D., Sweeney, L.M., Morris, J.B., Jarabek, A.M., 2015. Advances in inhalation dosimetry models and methods for occupational risk assessment and exposure limit derivation. Journal of Occupational and Environmental Hygiene 12, S18–S40.
Kusaka, Y., Iki, M., Kumagai, S., Goto, S., 1996. Epidemiological study of hard metal asthma. Occupational and Environmental Medicine 53, 188.
Lamon, L., Aschberger, K., Asturiol, D., Richarz, A., Worth, A., 2019. Grouping of nanomaterials to read-across hazard endpoints: A review. Nanotoxicology 13, 100–118.
Langård, S., 1994. Nickel-related cancer in welders. Science of the Total Environment 148, 303–309.
Lees, R.E.M., 1980. Changes in lung function after exposure to vanadium compounds in fuel oil ash. British Journal of Industrial Medicine 37, 253.
Leonard, S.S., Chen, B.T., Stone, S.G., *et al*., 2010. Comparison of stainless and mild steel welding fumes in generation of reactive oxygen species. Particle and Fibre Toxicology 7, 32.
Lippmann, M., Schlesinger, R.B., 1984. Interspecies comparisons of particle deposition and mucociliary clearance in tracheobronchial airways. Journal of Toxicology and Environmental Health 13, 441–469.
Liu, F., Wang, X.-Y., Zhou, X.-P., *et al*., 2017. Cadmium disrupts autophagic flux by inhibiting cytosolic Ca2 + -dependent autophagosome-lysosome fusion in primary rat proximal tubular cells. Toxicology 383, 13–23.
Löndahl, J., Massling, A., Pagels, J., *et al*., 2007. Size-resolved respiratory-tract deposition of fine and ultrafine hydrophobic and hygroscopic aerosol particles during rest and exercise. Inhalation Toxicology 19, 109–116.
Löndahl, J., Möller, W., Pagels, J.H., *et al*., 2013. Measurement techniques for respiratory tract deposition of airborne nanoparticles: A critical review. Journal of Aerosol Medicine and Pulmonary Drug Delivery 27, 229–254.
Luglio David, G., Katsigeorgis, M., Hess, J., *et al*., 2021. PM2.5 concentration and composition in subway systems in the Northeastern United States. Environmental Health Perspectives 129, 027001.
Marques, M.M., De Gonzalez, A.B., Beland, F.A., *et al*., 2019. Advisory group recommendations on priorities for the IARC monographs. The Lancet Oncology 20, 763–764.
McClellan, R.O., Henderson, R.F., 1995. Concepts In Inhalation Toxicology. Taylor & Francis Group: CRC Press.
Méndez, L.B., Gookin, G., Phalen, R.F., 2010. Inhaled aerosol particle dosimetry in mice: A review. Inhalation Toxicology 22, 15–20.
Miller, F.J., Asgharian, B., Schroeter, J.D., Price, O., 2016. Improvements and additions to the multiple path particle dosimetry model. Journal of Aerosol Science 99, 14–26.
Miller, F.J., Gardner, D.E., Graham, J.A., *et al*., 1979. Size considerations for establishing a standard for inhalable particles. Journal of the Air Pollution Control Association 29, 610–615.
Moulin, J.J., 1997. A meta-analysis of epidemiologic studies of lung cancer in welders. Scandinavian Journal of Work, Environment & Health 23, 104–113.
NIOSH, 2011. Occupational Exposure to Titanium Dioxide: Current Intelligence Bulletin 63. The National Institute for Occupational Safety and Health,U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.
NIOSH, 2021. Health Effects of Occupational Exposure to Silver Nanomaterials: Current Intelligence Bulletin 70. The National Institute for Occupational Safety and Health,U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.
NIOSH NPG, 2023. NIOSH Pocket Guide to Chemical Hazards (NPG), [Online]. The National Institute for Occupational Safety and Health, The Centers for Disease Control and Prevention. Available: https://www.cdc.gov/niosh/npg/ (Accessed 09/06 2023).
Nordberg, G.F., Costa, M., 2021a. Handbook on the Toxicology of Metals: Volume I: General Considerations. Academic press.
Nordberg, G.F., Costa, M., 2021b. Handbook on the Toxicology of Metals: Volume II: Specific Metals. Academic Press.
Nordberg, G.F., Nogawa, K., Nordberg, M., 2015. Chapter 32 - Cadmium. In: Nordberg, G.F., Fowler, B.A., Nordberg, M. (Eds.), Handbook on the Toxicology of Metals, fourth ed. San Diego: Academic Press.
Olsson, A., Kromhout, H., 2021. Occupational cancer burden: The contribution of exposure to process-generated substances at the workplace. Molecular Oncology 15, 753–763.
OSHA, 2011. National Emphasis Program – Primary Metal Industries. Occupational Safety and Health Administration, United States Department of Labor.
OSHA, 2023. Toxic metals [Online]. Occupational Safety and Health Administration, United States Department of Labor. Available: https://www.osha.gov/toxic-metals (Accessed 09/06 2023).
Palmer, K.T., Poole, J., Ayres, J.G., *et al*., 2003. Exposure to metal fume and infectious pneumonia. American Journal of Epidemiology 157, 227–233.
Pattanaik, S., Huggins, F.E., Huffman, G.P., 2016. The variability in iron speciation in size fractionated residual oil fly ash particulate matter (ROFA PM). Science of The Total Environment 562, 898–905.
Phalen, R.F., Mendez, L.B., 2009. Dosimetry considerations for animal aerosol inhalation studies. Biomarkers 14, 63–66.
Pritchard, R.J., Ghio, A.J., Lehmann, J.R., *et al*., 1996. Oxidant generation and lung injury after particulate air pollutant exposure increase with the concentrations of associated metals. Inhalation Toxicology 8, 457–477.
Purdue, M.P., Hutchings, S.J., Rushton, L., Silverman, D.T., 2015. The proportion of cancer attributable to occupational exposures. Annals of Epidemiology 25, 188–192.
Racette, B.A., 2014. Manganism in the 21st century: The Hanninen lecture. NeuroToxicology 45, 201–207.
Rachmawati, D., Bontkes, H.J., Verstege, M.I., *et al*., 2013. Transition metal sensing by Toll-like receptor-4: Next to nickel, cobalt and palladium are potent human dendritic cell stimulators. Contact Dermatitis 68, 331–338.

Rana, S., 2020. Endoplasmic reticulum stress induced by toxic elements—a review of recent developments. Biological Trace Element Research 196, 10–19.
Roberts, J.R., Young, S.-H., Castranova, V., Antonini, J.M., 2009. The soluble nickel component of residual oil fly ash alters pulmonary host defense in rats. Journal of Immunotoxicology 6, 49–61.
Robertson, A.J., Rivers, D., Nagelschmidt, G., Duncumb, P., 1961. STANNOSIS: Benign Pneumoconiosis due to Tin Dioxide. The Lancet 277, 1089–1093.
Sager, T.M., Kommineni, C., Castranova, V., 2008. Pulmonary response to intratracheal instillation of ultrafine versus fine titanium dioxide: Role of particle surface area. Particle and Fibre Toxicology 5, 17.
Sahoo, K., Sharma, A., 2023. Understanding the mechanistic roles of environmental heavy metal stressors in regulating ferroptosis: Adding new paradigms to the links with diseases. Apoptosis 28, 277–292.
Saletore, Y., Meyer, K., Korlach, J., *et al.*, 2012. The birth of the Epitranscriptome: deciphering the function of RNA modifications. Genome Biology 13, 1–12.
Salnikow, K., Zhitkovich, A., 2008. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: Nickel, arsenic, and chromium. Chemical Research in Toxicology 21, 28–44.
Santamaria, A.B., Sulsky, S.I., 2010. Risk assessment of an essential element: Manganese. Journal of Toxicology and Environmental Health, Part A 73, 128–155.
Sarlo, K., Baccam, M., 2007. Respiratory Allergy and Occupational Asthma
Schaich, K., 1992. Metals and lipid oxidation. Contemporary issues. Lipids 27, 209–218.
Schiller, C.F., Gebhart, J., Heyder, J., Rudolf, G., Stahlhofen, W., 1988. Deposition of monodisperse insoluble aerosol particles in the 0.005 to 0.2 μm size range within the human respiratory tract. Inhaled Particles VI. Elsevier.
Schlesinger, R.B., 1985. Comparative deposition of inhaled aerosols in experimental animals and humans: A review. Journal of Toxicology and Environmental Health 15, 197–214.
Schlesinger, R.B., 1989. Deposition and Clearance of Inhaled Particles
Schmidt, M., Goebeler, M., 2015. Immunology of metal allergies. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 13, 653–659.
Schmidt, M., Raghavan, B., Müller, V., *et al.*, 2010. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. Nature Immunology 11, 814–819.
Schubauer-Berigan, M.K., Dahm, M.M., Erdely, A., *et al.*, 2018. Association of pulmonary, cardiovascular, and hematologic metrics with carbon nanotube and nanofiber exposure among U.S. workers: A cross-sectional study. Particle and Fibre Toxicology 15, 22.
Sherwood, C.L., Lantz, R.C., Boitano, S., 2012. Chronic arsenic exposure in nanomolar concentrations compromises wound response and intercellular signaling in airway epithelial cells. Toxicological Sciences 132, 222–234.
Siew, S.S., Kauppinen, T., Kyyrönen, P., Heikkilä, P., Pukkala, E., 2008. Exposure to iron and welding fumes and the risk of lung cancer. Scandinavian Journal of Work, Environment & Health 34, 444–450.
Sizar, O., Talati, R., 2022. Berylliosis. Treasure Island (FL): StatPearls Publishing.
Sjoberg, S.G., 1954. Vanadium Bronchitis From Cleaning Oil-Fired Boilers. Nordisk Hygienisk Tidskrift, pp. 45-57
Smith, M.T., Guyton, K.Z., Gibbons, C.F., *et al.*, 2016. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Environmental Health Perspectives 124, 713–721.
Smyth, H.D., Hickey, A.J., 2011. Controlled Pulmonary Drug Delivery. Springer Science & Business Media.
Sørensen, A.R., Thulstrup, A.M., Hansen, J., *et al.*, 2007. Risk of lung cancer according to mild steel and stainless steel welding. Scandinavian Journal of Work, Environment & Health. 379–386.
Spyratos, D., Zarogoulidis, P., Porpodis, K., *et al.*, 2013. Occupational exposure and lung cancer. Journal of Thoracic Disease 5 (Suppl 4), S440–S445.
Straif, K., Cohen, A., Samet, J., 2010. Air pollution and cancer. IARC Scientific Publication. 161.
Sunderman, F.W., 2001. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Annals of Clinical & Laboratory Science 31, 3–24.
Tang, D., Chen, X., Kroemer, G., 2022. Cuproptosis: A copper-triggered modality of mitochondrial cell death. Cell Research 32, 417–418.
Tchounwou, P.B., Yedjou, C.G., Patlolla, A.K., Sutton, D.J., 2012. Heavy metal toxicity and the environment. Molecular, Clinical and Environmental Toxicology 3, 133–164. (environmental toxicology).
Templeton, D.M., 2015. Speciation in metal toxicity and metal-based therapeutics. Toxics 3, 170–186.
Thierse, H.-J., Gamerdinger, K., Junkes, C., Guerreiro, N., Weltzien, H.U., 2005. T cell receptor (TCR) interaction with haptens: Metal ions as non-classical haptens. Toxicology 209, 101–107.
Thomas, D.G., Smith, J.N., Thrall, B.D., *et al.*, 2018. ISD3: A particokinetic model for predicting the combined effects of particle sedimentation, diffusion and dissolution on cellular dosimetry for in vitro systems. Particle and Fibre Toxicology 15, 1–22.
Turner, M., Golovko, V.B., Vaughan, O.P.H., *et al.*, 2008. Selective oxidation with dioxygen by gold nanoparticle catalysts derived from 55-atom clusters. Nature 454, 981–983.
Utembe, W., Potgieter, K., Stefaniak, A.B., Gulumian, M., 2015. Dissolution and biodurability: Important parameters needed for risk assessment of nanomaterials. Particle and Fibre Toxicology 12, 1–12.
Vareille, M., Kieninger, E., Edwards, M.R., Regamey, N., 2011. The airway epithelium: Soldier in the fight against respiratory viruses. Clinical Microbiology Reviews 24, 210–229.
Wang, Z., Uddin, M.B., Xie, J., *et al.*, 2022. Chronic hexavalent chromium exposure upregulates the RNA methyltransferase METTL3 expression to promote cell transformation, cancer stem cell-like property, and tumorigenesis. Toxicological Sciences 187, 51–61.
Wild, P., Bourgkard, E., Paris, C., 2009. Lung cancer and exposure to metals: The epidemiological evidence. In: Verma, M. (Ed.), Cancer Epidemiology: Modifiable Factors. Totowa, NJ: Humana Press.
Wu, K.-G., Chang, C.-Y., Yen, C.-Y., Lai, C.-C., 2019. Associations between environmental heavy metal exposure and childhood asthma: A population-based study. Journal of Microbiology, Immunology and Infection 52, 352–362.
Wu, X., Cobbina, S.J., Mao, G., *et al.*, 2016. A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environmental Science and Pollution Research 23, 8244–8259.
Wyers, H., 1946. Some toxic effects of vanadium pentoxide. British Journal of Industrial Medicine 3, 177–182.
Xiong, S., George, S., Ji, Z., *et al.*, 2013. Size of TiO2 nanoparticles influences their phototoxicity: An in vitro investigation. Archives of Toxicology 87, 99–109.
Yang, C., Wang, Z., 2022. The epitranscriptomic mechanism of metal toxicity and carcinogenesis. International Journal of Molecular Sciences 23, 11830.
Yokel, R.A., Lasley, S.M., Dorman, D.C., 2006. The speciation of metals in mammals influences their toxicokinetics and toxicodynamics and therefore human health risk assessment. Journal of Toxicology and Environmental Health, Part B 9, 63–85.
Zeidler-Erdely, P.C., Erdely, A., Antonini, J.M., 2012. Immunotoxicology of arc welding fume: Worker and experimental animal studies. Journal of Immunotoxicology 9, 411–425.
Zeidler-Erdely, P.C., Falcone, L.M., Antonini, J.M., 2019. Influence of welding fume metal composition on lung toxicity and tumor formation in experimental animal models. Journal of Occupational and Environmental Hygiene 16, 372–377.
Zeidler-Erdely, P.C., Falcone, L.M., Antonini, J.M., *et al.*, 2020. Tumorigenic response in lung tumor susceptible A/J mice after sub-chronic exposure to calcium chromate or iron (III) oxide. Toxicology Letters 334, 60–65.
Zeidler-Erdely, P.C., Kashon, M.L., Battelli, L.A., *et al.*, 2008. Pulmonary inflammation and tumor induction in lung tumor susceptible A/J and resistant C57BL/6J mice exposed to welding fume. Particle and Fibre Toxicology 5, 12.

Zhang, H., Ji, Z., Xia, T., *et al*., 2012. Use of metal oxide nanoparticle band gap to develop a predictive paradigm for oxidative stress and acute pulmonary inflammation. ACS Nano 6, 4349–4368.

Zhao, D., Aravindakshan, A., Hilpert, M., *et al*., 2020. Metal/metalloid levels in electronic cigarette liquids, aerosols, and human biosamples: A systematic review. Environmental Health Perspectives 128, 036001.

Zhu, Y., Costa, M., 2020. Metals and molecular carcinogenesis. Carcinogenesis 41, 1161–1172.

Zychowski, K.E., Kodali, V., Harmon, M., *et al*., 2018. Respirable uranyl-vanadate-containing particulate matter derived from a legacy uranium mine site exhibits potentiated cardiopulmonary toxicity. Toxicological Sciences 164, 101–114.

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