Annotated Bibliography: Health Impacts of Exposure to Non-Mercury Hazardous Metals

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Purpose

The purpose of this project is to review the published literature from the last 10 years on the human health effects of toxic metals (excluding mercury [Hg]) emitted by coal-fired power plants. The studies primarily focus on the inhalation pathway but also include other exposure pathways or multi pathway exposures. Of specific interest were the following chemicals: arsenic, beryllium, cadmium, chromium, cobalt, manganese, nickel, lead, antimony, selenium, uranium, and vanadium.

Methods

Four separate searches were conducted on the scientific literature database PubMed (https://pubmed.ncbi.nlm.nih.gov/) to find relevant articles on the health effects of toxic non-Hg metals published between 2013 and 2023. The searches were separated into four categories based on the focus of what each search was trying to find (Table 1).

Table 1: Search terms for literature review.

Purpose of search	Search Terms	Search Date	No. of Returned Articles
Health effects of metals from coal burning power plants	("power plant" or “coal-fired” or "electricity generating unit" or coal burning) and (metal or inorganic or arsenic or beryllium or cadmium or chromium or cobalt or manganese or nickel or lead or antimony or selenium or uranium or and vanadium) and ("human health" or “health effects” or health)	5/12/23	624

Health effects of metals through inhalation exposure	(metal or inorganic or arsenic or beryllium or cadmium or chromium or cobalt or manganese or nickel or Pb or antimony or selenium or uranium or vanadium) and exposure and ("human health" or "health effects" or health) and inhalation NOT (tobacco or cigarette or pesticide or “personal care” or plastic or cosmetics) NOT (occupational or worker) NOT (nuclear or radiation)	5/16/23	676
Toxicology studies focused on inhalation of metals	(metal or arsenic or beryllium or cadmium or chromium or cobalt or manganese or nickel or Pb or antimony or selenium or uranium or vanadium) and exposure and (toxicology or toxicity) and inhalation NOT (tobacco or cigarette or pesticide or “personal care” or plastic or cosmetics) NOT (occupational or worker) NOT (nuclear or radiation)	5/16/23	551
Epidemiology studies focused on inhalation of metals	(metal or arsenic or beryllium or cadmium or chromium or cobalt or manganese or nickel or Pb or antimony or selenium or uranium or vanadium) and exposure and epidemiology and inhalation NOT (tobacco or cigarette or pesticide or "personal care" or plastic or cosmetics) NOT (occupational or worker) NOT (nuclear or radiation)	5/18/23	70

In conducting the searches, I optimized the search terms to include too many rather than too few articles. I included “NOT” terms to exclude studies that were irrelevant, primarily based on exposure (from personal use products, pesticides, nuclear power plants, etc.). I downloaded all 1,921 articles into the reference manager software Zotero and removed duplicate entries. I then filtered the articles first by title, then by abstract, and finally by reading the contents of the entire articles themselves. After title & abstract screening, 189 articles remained. Some articles that passed title & abstract screening were also deemed to be irrelevant. In addition, time constraints near the end of the

project timeline led to removing some articles as well. In the end, **98 articles** were summarized.

I included articles if they incorporated information on exposure to a specific metal (or metals) linked to developing health effects. Review articles were also included. I excluded articles if they failed to reference either a specific metal exposure or development of a health endpoint. I also excluded articles if they focused on exposure from non-coal sources, biological pathways or mechanisms of toxicity, policy, method development (e.g. new assays), or applying metals as treatment to a disease. I also removed articles that could not be obtained or were not in English. Due to these exclusion criteria, many epidemiology studies on health risks and general particulate matter (PM) exposure (unless they looked into PM composition) were excluded.

Annotated Bibliography

1. **Ahamed, M., Akhtar, M. J., Alhadlaq, H. A. & Alrokayan, S. A. Assessment of the lung toxicity of copper oxide nanoparticles: current status. *Nanomedicine (Lond)* 10, 2365–2377 (2015).**

Copper oxide nanoparticles (CuO NP) toxicity studies were reviewed by the authors. CuO NP were found to be cytotoxic and genotoxic in *in vitro* studies on human lung and larynx cells, likely mediated through reactive oxygen species (ROS) generation. In *in vivo* studies on rats exposed to CuO NP by intratracheal instillation, severe pulmonary toxicity was observed that included neoplastic lesions in lungs and fibrosis & granuloma formation in lungs. However, no studies were found in the literature regarding CuO NP toxicity via inhalation.

2. **Al Samri, M. T. *et al.* Lung toxicities of core-shell nanoparticles composed of carbon, cobalt, and silica. *Int J Nanomedicine* 8, 1223–1244 (2013).**

Cobalt (Co) nanoparticle exposure *in vitro* studies were conducted on mice lung tissue and *in vivo* studies were conducted on mice via intratracheal instillation. Multiple nanoparticle types were investigated, including carbon-cobalt-silica (C-Co-SiO_2) and carbon-cobalt oxide-silica (C-Co_3O_4-SiO_2) NP. *In vitro* studies showed that both Co NP impaired lung tissue bioenergetics and *in vivo* studies revealed additional negative effects on lung cells (alveolar wall necrosis with multiple apoptotic bodies). However, C-Co-SiO_2 toxicity appeared somewhat worse, possibly due to more Co being released into solution.

3. **Amster, E. Public health impact of coal-fired power plants: a critical systematic review of the epidemiological literature. *Int J Environ Health Res* 31, 558–580 (2021).**

The authors reviewed the epidemiological literature on the impact of coal-fired power plant emissions on morbidity and mortality. Three of forty articles related direct health effects from metals due to power plant metal emissions. In a population-based case-control study,

Persch et al. (2002) found that participants residing in the same district as power plants had significantly higher incidence of non-melanoma skin carcinoma than the national incidence rate attributed to arsenic emissions, dietary consumption, and occupational exposure. Li et al. (2017) found positive correlations between copper (Cu) and zinc (Zn) emissions from coal combustion and mortality in China between 1995-2014. Tang et al. (2008) showed umbilical cord blood lead was inversely associated with social and average developmental quotients.

4. **Amster, E. & Lew Levy, C. Impact of Coal-fired Power Plant Emissions on Children's Health: A Systematic Review of the Epidemiological Literature.** ***Int J Environ Res Public Health*** **16, (2019).**

The authors reviewed the epidemiological literature on the impact of coal-fired power plant emissions on children's health. One of seventeen articles focused on children's metal exposure and health outcomes. Tang et al. (2008) measured lead (Pb) in umbilical cord blood in a cohort of 133 maternal-infant pairs living within 2.5 km of a power plant in Chongqing, China prior to its closure in 2004. Cord Pb was inversely associated with social and average developmental quotients measured at age 2 using the Gesell Developmental Schedules.

5. **Assadian, E.** ***et al.*** **Toxicity of Copper Oxide (CuO) Nanoparticles on Human Blood Lymphocytes.** ***Biol Trace Elem Res*** **184, 350–357 (2018).**

The objective of this *in vitro* study was to determine the cytotoxicity of CuO NP on human blood lymphocytes. Blood lymphocytes were incubated for six hours at differing concentrations of CuO NP. CuO NP were found to be cytotoxic and the decreased viability of lymphocytes depended on concentration. CuO NP induced cell death due to ROS generation causing oxidative damage to the lymphocytes by NP penetration into the cell. In addition, CuO NP caused damage to mitochondria and lysosome organelles inside of the cell.

6. **Bai, A.-M. *et al.* Investigation Into Environmental Selenium and Arsenic Levels and Arseniasis Prevalence in an Arsenic-Affected Coal-Burning Area. *Front Nutr* 9, 922481 (2022).**

This epidemiological study aimed to explore the relationship between selenium (Se) levels in the environment and As poisoning in southern Shaanxi Province, China. A cohort of 50 patients older than 40 years who had lived in the high-As coal area for at least 1 year were recruited and compared to 50 healthy patients living in area without As poisoning. The results indicate that Se in hair and urine were negatively correlated with As poisoning and Se in the body was negatively correlated with the degree of As poisoning.

7. **Barn, P. *et al.* Coal smoke, gestational cadmium exposure, and fetal growth. *Environ Res* 179, 108830 (2019).**

This study focused on investigating gestational cadmium (Cd) exposure and fetal growth in Ulaanbaatar, Mongolia and was part of a randomized control trial. Cd concentrations were measured in 374 participants' blood during the third trimester of their pregnancy and children's birth outcomes were measured. The authors found that doubling blood Cd levels was associated with a 95g reduction in birth weight in regression models. This study was performed to investigate the effect of coal smoke from home cooking as a source of cadmium exposure.

8. **Blum, J. L., Edwards, J. R., Prozialeck, W. C., Xiong, J. Q. & Zelikoff, J. T. Effects of Maternal Exposure to Cadmium Oxide Nanoparticles During Pregnancy on Maternal and Offspring Kidney Injury Markers Using a Murine Model. *J Toxicol Environ Health A* 78, 711–724 (2015).**

This toxicology study aimed to understand the effects of cadmium oxide (CdO) NP on kidneys during pregnancy. Pregnant mice were exposed to CdO NP during gestational times representative of sensitive human pregnancy time windows and mice dam and neonate kidneys

were collected and examined for kidney injury biomarkers. Exposure resulted in renal injury (increase in kidney injury molecule-1 [Kim-1]) and increased mRNA expression in both adults and offspring, suggesting a potential cross-generational risk. Mammary glands were observed as a preferential site for Cd deposition during pregnancy, suggesting lactation as a possible neonate route of exposure.

9. **Borm, P. J. A., Fowler, P. & Kirkland, D. An updated review of the genotoxicity of respirable crystalline silica. *Part Fibre Toxicol* 15, 23 (2018).**

The authors reviewed 17 papers on genotoxicity related to respirable crystalline silica. While *in vitro* data showed inconsistent results, the *in vivo* data suggest an indirect mode of action for genotoxic effects. The studies found persistent inflammation leading to antioxidant responses in mice & rats, but DNA damage only in rats. The overall results supported earlier studies on the genotoxic and carcinogenic effects of silica inhalation and suggested a lower no-observed effect level of 5 ug/cm^2 (opposed to a previous threshold of 60-70 ug/cm^2). One study on occupational exposure in male workers indicated a genotoxic dose-response relationship.

10. **Boskabaddy, M. H. & Farkhondeh, T. Inhaled lead exposure affects tracheal responsiveness and lung inflammation in guinea pigs during sensitization. *Biol Trace Elem Res* 154, 363–371 (2013).**

This toxicology study focused on examining how lead exposure affects respiratory health. Guinea pigs were exposed to lead acetate via inhalation. The results indicated a greater increase in tracheal responsiveness, total white blood cell count, and decreased lymphocyte count among other effects associated with increased lung inflammation. The authors also observed a concentration-dependent increase in lung tissue Pb concentration and an association between blood Pb concentration and bronchial hyper-responsiveness. Subsequently, the authors conclude that lead exposure may increase the severity of asthma development.

11. **Boskabady, M. H., Tabatabai, S. A. & Farkhondeh, T. Inhaled lead affects lung pathology and inflammation in sensitized and control guinea pigs. *Environ Toxicol* 31, 452–460 (2016).**

This toxicology study found that guinea pigs exposed to lead via inhalation induced respiratory changes similar to asthma. Nine groups of 66 guinea pigs were exposed to lead acetate for an hour three times a week for two weeks. After examining lung tissue, serum inflammatory mediator (ET-1<, EPO, NO) levels were found to be significantly higher in the lead exposed group compared to the control group. These results indicate that lead may aggravate asthma severity both during development and after manifestation.

12. **Burzlaff, A. *et al.* A tiered approach to investigate the inhalation toxicity of cobalt substances. Tier 4: Effects from a 28-day inhalation toxicity study with tricobalt tetraoxide in rats. *Regul Toxicol Pharmacol* 130, 105129 (2022).**

This toxicology study focused on long term exposure of rats to Co exposure via inhalation. Rats exposed to 28 days of tricobalt tetraoxide (Co_3O_4) exhibited concentration-dependent increases in inflammatory cells (including neutrophils) and these elevated levels persisted 90 days after exposure ceased. Exposure-related effects were limited to the respiratory system although a multitude of organs were histopathologically examined. Larynx metaplasia was observed but no genotoxicity was detected.

13. **Canfield, R. L., Jusko, T. A. & Radegonde, V. Airborne particulate lead and children's mental functioning. *Neurotoxicology* 81, 288–293 (2020).**

This paper focused on the effects of Pb toxicity on children. The results of four meta-analyses found that a 10 ug/dl increase in blood Pb levels was associated with a 1-5 point decrease in IQ on the Stanford-Binet test. The pattern observed also suggests that there is a non-linear exposure-response function. Furthermore, no children's Pb exposure study has shown a threshold level below which there are no effects. Other effects observed in adults &

children include lethargy, cramping, anemia, peripheral neuropathy, confusion, coma, seizures, and death.

14. Cervantes-Valencia, M. E., González-Villalva, A., Cano-Gutiérrez, G., Albarrán-Alonso, J. C. & Fortoul, T. I. Effects of Vanadium Inhalation and Sweetened Beverage Ingestion in Mice: Morphological and Biochemical Changes in the Liver. *Int J Toxicol* 40, 466–474 (2021).

This toxicology study demonstrated that vanadium (V) inhalation and sweetened beverage ingestion co-exposure induced liver damage due to oxidative stress. Mice were exposed to V_2O_5 for 1 hour twice a week during 4 and 8 weeks at a concentration of 1436 ug V/m^3. Results indicated an increase in hepatic enzymes, De Ritis ratio, and steatosis in exposed mice, as well as binucleated cells and meganuclei.

15. Cervantes-Yépez, S., López-Zepeda, L. S. & Fortoul, T. I. Vanadium inhalation induces retinal Müller glial cell (MGC) alterations in a murine model. *Cutan Ocul Toxicol* 37, 200–206 (2018).

This toxicology study demonstrated that V inhalation induced retinal damage in mice likely due to oxidative stress. Mice inhaled V for 1 hour twice a week at 4 and 8 weeks at concentrations of 1.4 mg V/m^3. The authors suggest that the morphological changes observed in the retina were a result of systemic distribution of V and not due to direct eye contact. Photoreceptor degeneration due to V inhalation was also related to time of V exposure.

16. Chau, B., Witten, M. L., Cromey, D., Chen, Y. & Lantz, R. C. Lung developmental is altered after inhalation exposure to various concentrations of calcium arsenate. *Toxicol Appl Pharmacol* 432, 115754 (2021).

This toxicology study demonstrated that arsenic (As) inhalation during lung development altered lung function and structure in a dose dependent manner. Mice were exposed via inhalation to dust containing 3% or 10% of calcium arsenate during the in utero and early

postnatal life stages. Exposed mice were observed to have significant increases in pulmonary baseline resistance, airway hyperreactivity, and airway collagen and smooth muscle expression.

17. **Chen, H. *et al.* Effects of air pollution on human health - Mechanistic evidence suggested by in vitro and in vivo modelling. *Environ Res* 212, 113378 (2022).**

This paper reviewed the effects of oxidative stress and inflammatory response by particulate matter (PM). PM containing metals trigger inflammatory responses in multiple organs including lungs, brain, liver, and organs in the cardiovascular system. The urinary system is also highly susceptible to heavy metals and occupational exposure has been associated with renal tubular and interstitial damage.

18. **Colín-Barenque, L. *et al.* Functional and morphological olfactory bulb modifications in mice after vanadium inhalation. *Toxicol Pathol* 43, 282–291 (2015).**

This toxicology study found that V inhalation impaired olfactory function. Forty mice were exposed to 0.02M V_2O_5 for one hour, two times per week, for four weeks. Their olfactory function was evaluated based on the buried food test. Results showed that V inhalation resulted in altered olfactory histological, ultrastructural, and enzymatic activity as early as two weeks due to a loss of dendritic spine and granule cell death. V caused oxidative stress that resulted in neuronal death by apoptosis and necrosis and V may be a risk factor for neurodegenerative diseases like Parkinson's and Alzheimers'.

19. **Cooper, K. L., Liu, R. & Zhou, X. Particulate arsenic trioxide induces higher DNA damage and reactive oxygen species than soluble arsenite in lung epithelial cells. *Toxicol Appl Pharmacol* 457, 116320 (2022).**

This *in vitro* study found that arsenic trioxide exposure yields higher oxidative DNA damage to lung epithelial cells than soluble AsIII. Epithelial cells were exposed to 0.3-10 uM particulate arsenic trioxide or 0.3-1 uM soluble AsIII for 1-24 hours and then analyzed. Particulate arsenic trioxide generated higher superoxide, peaking at 2 hours of exposure, and also had lower

cellular As uptake efficiency.

20. Cruz, N., Buscaglia, R., Salanga, M. & Kellar, R. Environmentally Relevant Levels of Depleted Uranium Impacts Dermal Fibroblast Proliferation, Viability, Metabolic Activity, and Scratch Closure. *Toxics* 9, (2021).

This *in vitro* study found that dermal cells exposed to uranium (U) resulted in negative effects on cellular metabolism and physiology. Human neonatal dermal fibroblasts were exposed to 0.1-100 uM uranyl nitrate ($UO_2(NO_3)_2$) for 24-144 hours and were found to have significantly diminished metabolic activity proportional to increasing concentrations of uranyl nitrate up to 10 uM. The researchers observed deleterious outputs in cell membrane integrity, migration, proliferation, and doubling time, although no effects on proliferation rates. As a result, dermal contact with uranyl nitrate has the potential to affect wound healing and exacerbate pre-existing skin diseases.

21. Dai, L. *et al.* Elevated whole blood arsenic level is associated with type 2 diabetes in coal- burning areas in Guizhou. *Toxicol Appl Pharmacol* 403, 115135 (2020).

This case-control epidemiology study found a dose-dependent relationship between prolonged As exposure and increased risk of type 2 diabetes, even at low As levels. Higher blood As levels were associated with a high risk of type 2 diabetes in populations exposed to coal-burning As living in Yunnan-Guizhou Plateau, China. The authors paired 232 subjects with type 2 diabetes with 232 healthy subjects based on gender and age. The results showed a nonlinear, threshold effect in which blood As levels less than 3.29 ug/L may be considered safe. Additionally, the authors saw a higher risk for type 2 diabetes among long-term smokers also exposed to As.

22. Das, A., Habib, G., Perumal, V. & Kumar, A. Estimating seasonal variations of realistic exposure doses and risks to organs due to ambient particulate matter -bound metals of

Delhi. *Chemosphere* 260, 127451 (2020).

The aim of this study was to calculate deposition of three PM-associated carcinogenic metals (As, Pb, and Cd) in organs following inhalation in Dehli, India. Deposition was modeled by integrating human respiratory tract and physiologically-based pharmacokinetic models for metal PM2.5 dissolution in lung fluid. Calculations showed Pb to primarily deposit in tissues such as bone, muscle, and blood. On the other hand, Cd mostly deposits in lungs and intestines, while As deposits primarily in lungs, muscle (liver), and skin.

23. Dumková, J. *et al.* Sub-chronic inhalation of lead oxide nanoparticles revealed their broad distribution and tissue-specific subcellular localization in target organs. *Part Fibre Toxicol* 14, 55 (2017).

This toxicology study found that lead inhalation exposure led to adverse effects in the lungs, liver, and kidneys. Mice were exposed to ~10^6 particles/cm^3 lead oxide nanoparticles (PbO NP) for six weeks and Pb was found in the kidney, lungs, liver, spleen, and brain after sacrifice. In the liver, excess lipid accumulation suggested toxic effects caused by hepatocyte hydropic degeneration/hypertrophy and focal necrosis. Inflammation was also observed in the renal cortex. The lungs were the most affected organ, exhibiting hyperaemia, alveolar emphysema, focal acute catarrhal bronchiolitis, and other adverse effects.

24. Dumkova, J. *et al.* Inhaled Cadmium Oxide Nanoparticles: Their in Vivo Fate and Effect on Target Organs. *Int J Mol Sci* 17, (2016).

This toxicology study focused on structural changes in the lungs, liver, kidneys, and spleen due to CdO NP exposure. Mice were exposed via inhalation to 2.96 x 10^6 particles/cm^3 for six weeks. Histopathological changes were visible in both the lungs' respiratory passages and alveoli; significant alterations included hyperemia, alveolar emphysema, and congested capillaries. In the liver, CdO NP exposure caused periportal inflammation and local cellular necrosis. In the kidneys, thickening of the filtration membrane was observed. Since Cd is

transported to secondary organs via blood circulation, the entire circulatory system may be potentially affected.

25. Dziubanek, G. *et al.* Long-term exposure to urban air pollution and the relationship with life expectancy in cohort of 3.5 million people in Silesia. *Sci Total Environ* 580, 1–8 (2017).

This epidemiology study focused on exploring the association between long-term inhalation of Cd and Pb (among other air pollutants) in Silesia province, Poland. The combined effect of inhaling PM10, benzo(a)pyrene, Cd, and Pb was significantly associated with reduced life expectancy in women and men. However, the relationship between exposure to heavy metals (Cd and Pb together or individually) was not significant. This may be either because inhalation is not an important route of exposure or because Cd and Pb concentrations are low in Silesia ambient air.

26. Eckard, M. L. *et al.* Neonatal exposure to ultrafine iron but not combined iron and sulfur aerosols recapitulates air pollution-induced impulsivity in mice. *Neurotoxicology* 94, 191–205 (2023).

This toxicology study explored whether developmental exposure to iron (Fe) aerosols affects neurological health. Mice were exposed postnatally via inhalation to 1.35 ug/m^3 Fe particle mass concentration across 8 days and then tested for behavior deficits in adulthood. Fe developmental exposure did not affect total locomotor activity or novel object recognition, but did impair impulsive-like and timing-based behaviors in adulthood. These results were primarily male-specific and dependent on whether Fe was exposed concurrently with sulfur dioxide (SO_2).

27. Egendorf, S. P., Gailey, A. D., Schachter, A. E. & Mielke, H. W. Soil toxicants that potentially affect children's health. *Curr Probl Pediatr Adolesc Health Care* 50, 100741 (2020).

This article summarized the health effects of some inorganic soil contaminants (As, Cd, and Pb) on children's health. Arsenic poisoning may cause gastrointestinal tract symptoms (nausea,

vomiting, diarrhea, etc.), skin lesions, neurological effects, cancer (skin, lung, and bladder), and other symptoms. Cadmium is an endocrine-disrupting chemical and may cause severe lung and kidney damage. Lead primarily influences brain and nervous system development in children.

28. **Espinosa-Zurutuza, M. *et al.* Oxidative Stress as a Mechanism Involved in Kidney Damage After Subchronic Exposure to Vanadium Inhalation and Oral Sweetened Beverages in a Mouse Model. *Int J Toxicol* 37, 45–52 (2018).**

This toxicology study found that mice inhaling V combined with ingesting 30% sucrose in drinking water induced functional and histological kidney damage and increased oxidative biomarkers. Inflammation caused by ROS were observed in the kidneys of the V only, sucrose only, and V + sucrose groups, but were most spread out in the combined group. Tubular modifications were observed although glomerular alterations were not, and hematuria was most severe in the combined V + sucrose group.

29. **Falcon-Rodriguez, C. I., De Vizcaya-Ruiz, A., Rosas-Pérez, I. A., Osornio-Vargas, Á. R. & Segura-Medina, P. Inhalation of concentrated PM(2.5) from Mexico City acts as an adjuvant in a guinea pig model of allergic asthma. *Environ Pollut* 228, 474–483 (2017).**

This toxicology study found that acute inhalation of fine particulate matter (PM2.5) can produce allergic asthma in sensitized guinea pigs, leading to bronchoconstriction, airway inflammation, and pulmonary damage. Guinea pigs inhaled ~609 ug/m^3 PM2.5 from Mexico City for 5 hours over 3 days. Guinea pigs were sensitized with Ovalbumin and aluminum hydroxide and only these sensitized groups produced biomarkers. While specific metal exposure was not isolated, particle composition analysis identified inorganic elements in the PM2.5 and hypothesized their role in acting as adjuvant.

30. **Farkhondeh, T., Boskabady, M. H., Jalali, S. & Bayrami, G. The effect of lead exposure on tracheal responsiveness to methacholine and ovalbumin, total and differential white blood cells count, and serum levels of immunoglobulin E, histamine, and cytokines in guinea pigs. *Hum Exp Toxicol* 33, 325–333 (2014).**

This toxicology study reported that exposure to lead acetate via inhalation can induce lung inflammatory changes in guinea pigs. Guinea pigs were exposed to differing concentrations of lead acetate (0.1, 0.2, or 0.4 M Pb concentration) for 1 hour, three times a week, for two weeks. Significant changes were not observed for guinea pigs in the 0.1 M group. However, differential white blood cell count, tracheal responsiveness, and inflammation were observed in the other groups. These results may link the possibility of asthma and other respiratory disorder developments with environmental Pb pollution.

31. Faroon, O., Keith, S., Mumtaz, M. & Ruiz, P. Minimal Risk Level Derivation for Cadmium: Acute and Intermediate Duration Exposures. *J Exp Clin Toxicol* 1, 1–12 (2017).

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a comprehensive literature review of Cd and developed a toxicological profile to identify minimal risk levels (MRLs) for Cd, above which health effects are expected to occur. ATSDR selected the National Toxicology Program's (NTP) toxicology study as the critical study for deriving the acute duration inhalation MRL. As such, the MRL was determined to be 0.03 ug Cd/m^3 based on alveolar histiocytic infiltration and focal inflammation in alveolar septa observed in all (male and female) rats. The critical study for intermediate oral MRL was derived from a study by Brzoska and Moniuszko (2005) based on skeletal alterations (decreased bone density) endpoints and determined to be 0.5 ug Cd/kg/d.

32. Feng, X. *et al.* Oxidative potential and water-soluble heavy metals of size-segregated airborne particles in haze and non-haze episodes: Impact of the 'Comprehensive Action Plan' in China. *Sci Total Environ* 814, 152774 (2022).

This *in vitro* study focused on exploring oxidative potential and water-soluble heavy metal levels in Beijing, China on haze and non-haze days. DNA damage was assessed by a plasmid scission assay. Calculated Pearon correlation coefficients between metal concentrations and DNA

damage were significantly positive for Pb, Cr, Cd, and Zn. For Cd and Zn, significant reductions in their mass concentrations and maximum/average DNA damage values were observed after Beijing implemented its Comprehensive Action Plan (CAP), demonstrating the effectiveness of this policy on restricting coal-burning emissions and improving air quality for human health.

33. Feng, X. *et al.* Particle-induced oxidative damage by indoor size-segregated particulate matter from coal-burning homes in the Xuanwei lung cancer epidemic area, Yunnan Province, China. *Chemosphere* 256, 127058 (2020).

This *in vitro* study collected and compared particulate matter from two locations in China (Hutou village, an area with high-risk lung cancer and Xize village, a low-risk comparison site) where coal is used for cooking to study the toxicological properties of particulates. The authors found a significant positive correlation for Zn, Cu, Cd, rubidium (Rb), thallium (Tl), caesium (Cs), and antimony (Sb) with particle-induced DNA damage rates. As a result, the mass concentration of these elements were hypothesized to drive the oxidative potential of particulate matter and could represent the health risk level of particulate matter exposure. Contrastingly, they also found that strontium (Sr) was negatively correlated with DNA damage and hypothesized that it may mediate DNA damage.

34. Gandamalla, D., Lingabathula, H. & Yellu, N. Nano titanium exposure induces dose- and size- dependent cytotoxicity on human epithelial lung and colon cells. *Drug Chem Toxicol* 42, 24–34 (2019).

This *in vitro* study found size- and dose-dependent cytotoxicity in human epithelial lung and colon cells exposed to titanium dioxide nanoparticles (Ti NPs).

35. Gandhi, D., Bhandari, S., Mishra, S., Tiwari, R. R. & Rajasekaran, S. Non-malignant respiratory illness associated with exposure to arsenic compounds in the environment. *Environ Toxicol Pharmacol* 94, 103922 (2022).

This literature review focused on current experimental and clinical studies of As exposure and non-malignant lung disease. *In vivo* and *in vitro* studies showed that As exposure may induce oxidative stress, apoptosis, inflammatory responses, epithelial-to-mesenchymal transition, airway dysfunction, and abnormal lung development. These adverse pulmonary function and inflammation effects were also seen in epidemiological studies, although men appeared to be more susceptible than women. *In utero* and early childhood exposure studies also demonstrated that maternal exposure to As was linked to spontaneous abortion, neonatal/infant mortality, reduced lung function, and chronic cough. Other studies found that As exposure may be related to allergic asthma and pulmonary tuberculosis.

36. Germande, O. *et al.* NiONP-Induced Oxidative Stress and Mitochondrial Impairment in an In Vitro Pulmonary Vascular Cell Model Mimicking Endothelial Dysfunction. *Antioxidants (Basel)* 11, (2022).

This in vitro study found that exposure to nickel oxide nanoparticles (NiO NPs) can reproduce pulmonary hypertension under physiological and pathological conditions. Under acellular conditions, NiO NPs generated ROS and nitrite, causing cytotoxicity. When cells were exposed under pathological conditions, higher observed oxidative stress in the mitochondria suggests that severe damage could be done to the endothelium. Increased nitrite production and pro-inflammatory responses also amplifies NiO NPs' toxic effects. As a result, NiO NPs may adversely affect populations with existing cardiovascular risks.

37. González Rendón, E. S., Cano, G. G., Alcaraz-Zubeldia, M., Garibay-Huarte, T. & Fortoul, T. I. Lead inhalation and hepatic damage: Morphological and functional evaluation in mice. *Toxicol Ind Health* 34, 128–138 (2018).

This toxicology study found that Pb inhalation exposure is linked to oxidative stress in the liver. Mice were exposed to 0.1 M lead acetate twice a week for 1 hour over 8 weeks. Histological changes in inflammatory infiltrate and meganuclei in the liver were observed since the first

week of exposure. The authors also observed significant decreases in hepatocyte survival and increases in the number and severity of pathological alterations. Blood and liver Pb concentrations increased beginning at week four, but decreased again when the exposure was suspended, suggesting that the liver can efficiently eliminate Pb.

38. Gosens, I. *et al.* Organ burden and pulmonary toxicity of nano-sized copper (II) oxide particles after short-term inhalation exposure. *Nanotoxicology* 10, 1084–1095 (2016).

This toxicology study found that inhalation exposure to CuO NP causes dose-dependent lung inflammation and cytotoxicity. Rats were exposed (nose-only) to varying doses of CuO NP for five consecutive days and found to exhibit a number of lung issues including alveolitis, bronchiolitis, vacuolation of the respiratory epithelium, and emphysema. Only limited inflammation was still observed after exposure was stopped and rats were allowed to recover over a period of 22 days. No histopathological changes were detected in other organs of interest (brain, olfactory bulb, spleen, kidney, and liver).

39. Gray, D. L., Wallace, L. A., Brinkman, M. C., Buehler, S. S. & La Londe, C. Respiratory and cardiovascular effects of metals in ambient particulate matter: a critical review. *Rev Environ Contam Toxicol* 234, 135–203 (2015).

This literature review looked at the effects of transition metals (As, chromium [Cr], Cu, Fe, Mn, Ni, Se, Ti, V, and Zn) on respiratory and cardiovascular health effects associated with ambient PM in epidemiology and toxicology studies. Studies found that Cu, Fe, Ni, V, and Zn exposure from ambient PM can produce acute inflammatory responses. However, the authors concluded that PM metals are not major contributors to health because the *in vivo* and *in vitro* studies both looked at concentrations much higher than ambient PM levels and the epidemiology studies did not focus on individual level exposure.

40. Guo, T. *et al.* Acute lung inflammation induced by zinc oxide nanoparticles: Evolution and intervention via NRF2 activator. *Food Chem Toxicol* 162, 112898 (2022).

This toxicology study found that exposure to zinc oxide nanoparticles (ZnO NP) leads to lung oxidative stress, cell injury, and inflammation. Mice were exposed to a single intratracheal instillation of 20 ug of ZnO NP. An inflammatory response associated with increased neutrophil and macrophage counts was observed three and seven days later. Mice exhibited rapid breathing, shortness of breath, decreased appetite, and reduced activity.

41. Hendryx, M., Zullig, K. J. & Luo, J. Impacts of Coal Use on Health. *Annu Rev Public Health* 41, 397–415 (2020).

This literature review explored the public health impacts of coal. Per kilowatt hour, coal combustion generates more heavy metals than other fossil fuels. Pollutants such as As and Cr have been associated with premature mortality, respiratory disease, poor child health, and other diseases.

42. Holan, V. *et al.* A murine model of the effects of inhaled CuO nanoparticles on cells of innate and adaptive immunity - a kinetic study of a continuous three-month exposure. *Nanotoxicology* 13, 952–963 (2019).

This toxicology study explored the effects of CuO NP on the immune system. Mice were continuously exposed to CuO NP by inhalation continuously for three months for an average deposited dose of 0.379 ug/g mouse body weight. Results showed that CuO NP significantly altered the composition of cell populations in the innate and adaptive immune system but changes were time-dependent.

43. Horton, L. M., Mortensen, M. E., Iossifova, Y., Wald, M. M. & Burgess, P. What do we know of childhood exposures to metals (arsenic, cadmium, lead, and mercury) in emerging market countries? *Int J Pediatr* 2013, 872596 (2013).

This literature review explored childhood exposure to As, Cd, and Pb in the International Monetary Fund's (IMF) top 10 emerging market countries. Childhood As exposure reported significant associations between As in blood or urine and precancerous skin lesions. Negative associations were reported between Cd cord blood and birth outcomes (birth height, weight, etc.). Additionally, negative associations were reported between blood lead levels and neurological,

behavioral, and mental development test scores similar to results reported in US studies.

44. Hossain, S., Latifa, G. A., Prianqa & Al Nayeem, A. Review of Cadmium Pollution in Bangladesh. *J Health Pollut* 9, 190913 (2019).

This literature review explored the sources, routes, and health impacts of Cd pollution in Bangladesh. Among health effects, the authors reported that Cd adversely affects the endocrine system, neuronal differentiation, and inhibits calcium transport to breast milk in mothers. Cd also affects bone metabolism, cancer, and brain development in children.

45. Hou, Y., Yan, W., Guo, L., Li, G. & Sang, N. Prenatal PM(2.5) exposure impairs spatial learning and memory in male mice offspring: from transcriptional regulation to neuronal morphogenesis. *Part Fibre Toxicol* 20, 13 (2023).

This toxicology study found that prenatal exposure to inorganic metals in PM2.5 were harmful to neuronal morphogenesis, indicating that they may negatively affect cognitive function in offspring. Pregnant mice were exposed to PM2.5 (3 mg/kg) via oropharyngeal aspiration every two days and their pups were evaluated. Thirty-one inorganic elements (including zinc, copper, lead, and manganese) were detected in the PM2.5 collected on a rooftop university building in Shanxi, China and used for exposure. While organic and inorganic PM2.5 extracts both inhibited neuronal growth, transcriptional regulation, and significantly decreased Hoxa5 levels, organic extracts (likely polycyclic aromatic hydrocarbons or PAHs) showed stronger effects than did the inorganic elements.

46. Hu, Y., Xiao, T., Wang, Q., Liang, B. & Zhang, A. Effects of Essential Trace Elements and Oxidative Stress on Endemic Arsenism Caused by Coal Burning in PR China. *Biol Trace Elem Res* 198, 25–36 (2020).

This epidemiology study investigated the association between essential trace elements and oxidative stress in environmental media and human populations with endemic arsenism in Guizhou

Province, China caused by burning coal. As, Cu, Fe, and Cr content in soil was significantly higher in the arsenism area than the control area, while Se content was significantly lower. Correlations between trace element content and oxidative stress indicators suggest that changes in these element concentrations in environmental media may induce oxidative stress. As a result, insufficient Se intake and Cu/Cr overload may be linked to pollution-induced arsenism.

47. Hu, Y., Xiao, T. & Zhang, A. Associations between and risks of trace elements related to skin and liver damage induced by arsenic from coal burning. *Ecotoxicol Environ Saf* 208, 111719 (2021).

This epidemiology study explored the association between trace elements and skin/liver damage induced by coal-burning As. Participants from two villages (one with high arsenism and a control village) in Guizhou Province, China were grouped by As exposure and hair and blood samples were taken. Skin damage was diagnosed by two dermatologists and liver function was analyzed. Overall, increases in aluminum (Al) and vanadium (V), as well as a decrease in Se was associated as risk factors for both As induced skin and liver damage. Logistic regression models found significant positive correlations between Cr, V, Al, Pb, and Cd and skin damage. V was also found to have a significant positive correlation with liver damage.

48. Islam, S., Kamila, S. & Chattopadhyay, A. Toxic and carcinogenic effects of hexavalent chromium in mammalian cells in vivo and in vitro: a recent update. *J Environ Sci Health C Toxicol Carcinog* 40, 282–315 (2022).

This literature review focused on the adverse effects of Cr(VI) on mammalian cells in *in vivo* and *in vitro* studies. Evidence found that Cr(VI) induces apoptosis, autophagy, chromatin condensation, DNA damage, and loss of mitochondrial functions that may increase cancer risks in humans. Multiple rat studies also found toxic effects on the reproductive and nervous systems.

49. Johns, C. E. *et al.* The Cd/Zn Axis: Emerging Concepts in Cellular Fate and Cytotoxicity.

Biomolecules **13, (2023).**

This article explores the biochemical, cellular, and tissue-specific toxic effects of Cd. Cd is listed as a Group I carcinogen by the International Agency for Research on Cancer (IARC) and affects the adaptive immune system by disrupting the DNA-repair system, deactivating tumor suppressor genes, and stimulating proto-oncogenes. Chronic exposure to Cd also increases the production of ROS, which can damage the lungs, kidneys, and bones. Zn plays an antagonizing role on the toxic effects of heavy metals, including Cd. On the other hand, Cd may elevate Zn deficiency.

50. Khalaf, E. M. *et al.* Relationship between exposure to heavy metals on the increased health risk and carcinogenicity of urinary tract (kidney and bladder). *Rev Environ Health* (2023) doi:10.1515/reveh-2022-0245.

This literature review explored the relationship between heavy metal exposure and increased carcinogenicity risk in the urinary tract (kidney and bladder). As, Pb, and V cause irreversible carcinogenic effects on various organs including the liver, pancreas, kidney, breast, and bladder. Exposure to As, Cr, Ni, Cd (and their metabolites) may mediate the overproduction of ROS that damages DNA. Studies included in this review suggested that metals enter the body through ingestion and inhalation.

51. Kittner, N., Fadadu, R. P., Buckley, H. L., Schwarzman, M. R. & Kammen, D. M. Trace Metal Content of Coal Exacerbates Air-Pollution-Related Health Risks: The Case of Lignite Coal in Kosovo. *Environ Sci Technol* 52, 2359–2367 (2018).

This study investigated the trace metal content of As, Hg, Cr, and Ni in Kosovo lignite coal and uses the ExternE method (Markandya and Wilkinson, 2007) to calculate deaths from air pollution related risk. This study does not separate metal induced deaths in its analysis. The authors found that significant trace metal content normalized per kWh of final electricity delivered was high, ranging from 19.7 mg/kWh for Ni to 44 mg/kWh for Cr. The authors also estimate that 2,300 premature deaths could be avoided in Kosovo by 2030 by switching to

alternative fuel sources.

52. Klocke, C. *et al.* Enhanced cerebellar myelination with concomitant iron elevation and ultrastructural irregularities following prenatal exposure to ambient particulate matter in the mouse. *Inhal Toxicol* 30, 381–396 (2018).

This toxicology study explored the association between prenatal exposure to concentrated ambient particles on the central nervous system and autism spectrum disorder. The authors observed Fe, Al, and silicon (Si) inclusions in the corpus callosum along with myelin sheath damage. These effects were sex-specific and affected males more than females. Particle composition revealed Mn, Fe, Ni, Cu, Zn, and Sr concentrations above normal atmospheric levels and lends to the potential for mixture-specific effects.

53. Kong, L. *et al.* Exposure effects of inhaled nickel nanoparticles on the male reproductive system via mitochondria damage. *NanoImpact* 23, 100350 (2021).

This toxicology study found male reproductive toxicity was associated with nickel nanoparticle (Ni NP) exposure by inhalation. Male mice were exposed to varying doses of Ni NP by intratracheal instillation. The authors observed decreased serum reproductive hormones and sperm count, increased serum inflammatory factors, sperm deformities and cell apoptosis, and pathological changes in mouse testes.

54. Krall, J. R., Hackstadt, A. J. & Peng, R. D. A hierarchical modeling approach to estimate regional acute health effects of particulate matter sources. *Stat Med* 36, 1461–1475 (2017).

The authors developed a hierarchical model (SHARE) that facilitates reproducible, multisite epidemiologic studies of PM sources. The authors then estimated regional-level health effects associated with short-term exposure to PM in the northeastern US. Same-day PM2.5 from metals were associated with increased emergency cardiovascular disease hospitalizations during the warm season.

55. Kravchenko, J. & Lyerly, H. K. The Impact of Coal-Powered Electrical Plants and

Coal Ash Impoundments on the Health of Residential Communities. ***N C Med J*** **79, 289–300 (2018).**

This literature review summarizes the health effects of metals related to coal-burning power plant emissions in Table 3. Pb leads to abdominal pain, memory loss, and neurodevelopmental effects. V is associated with tremor, cardiovascular symptoms (arrhythmia(, and lung carcinogenesis. Co is associated with cardiovascular and respiratory effects. Cr(VI) is associated with kidney/liver disease, lung cancer, and genotoxic effects.

56. Ku, T., Zhang, Y., Ji, X., Li, G. & Sang, N. PM(2.5)-bound metal metabolic distribution and coupled lipid abnormality at different developmental windows. ***Environ Pollut*** **228, 354–362 (2017).**

This toxicology study examined the metabolic distributions of six metals (Zn, Pb, Mn, As, Cu, and Cd) following PM2.5 inhalation in mice during differing developmental windows. PM2.5 was collected in Shanxi Province, China and mice at 4 weeks, 4 months, and 10 months received 3 mg/kg PM2.5 every other day for 4 weeks. Triglyceride and total cholesterol levels were then analyzed in the animals. Pb, Mn, As, and Cd were significantly correlated with total cholesterol levels in the heart, brain, liver/lung, respectively. These results indicate that PM2.5 produces adverse biological effects sensitive to differing developmental windows, potentiating the systemic toxicity of these metals.

57. Kulkarni, A., Kumar, G. S., Kaur, J. & Tikoo, K. A comparative study of the toxicological aspects of vanadium pentoxide and vanadium oxide nanoparticles. ***Inhal Toxicol*** **26, 772–788 (2014).**

This toxicology study explored the effects of V_2O_5 NP and VO_2 NP exposure via inhalation in rats. Rats were exposed to varying NP doses for six hours, five days per week for fourteen days. VO_2 NP exhibited higher toxicity than V_2O_5 NP. The authors observed fibrosis in the lung tissue, with an increase in surface collagen. Lung tissue showed high damage and

inflammatory response to VO_2 NP that persisted even a week past recovery.

58. Lai, X. *et al.* Intranasal Delivery of Copper Oxide Nanoparticles Induces Pulmonary Toxicity and Fibrosis in C57BL/6 mice. *Sci Rep* 8, 4499 (2018).

This toxicology study found that CuO NP aggravated pulmonary inflammation in a dose-dependent manner in mice. Mice were nasally instilled with CuO NP at six weeks old. CuO NP induced acute lung toxicity by DNA damage, ROS generation, and apoptosis in lung epithelial cells. In addition, authors observed that CuO NP induced infiltration of inflammatory cells and promoted myofibroblast activation and collagen deposition. As a result, CuO NP was linked to the potential development of pulmonary fibrosis.

59. Lebedová, J. *et al.* Impact of acute and chronic inhalation exposure to CdO nanoparticles on mice. *Environ Sci Pollut Res Int* 23, 24047–24060 (2016).

This toxicology study found that chronic inhalation of CdO NP created dose-dependent alterations in lung and liver morphology and damage to tissues. Mice were exposed to whole body inhalation for 4-72 hours (acute exposure) or 1-13 weeks (chronic exposure) of CdO NP. Oxidative stress increased lipid peroxidation and adverse effects only progressed with longer exposure duration. Although most CdO NP were deposited in the lungs, longer exposures redistributed CdO NP into the kidney, liver, and spleen starting at 72 hours of exposure.

60. Lebedová, J. *et al.* Impact of acute and subchronic inhalation exposure to PbO nanoparticles on mice. *Nanotoxicology* 12, 290–304 (2018).

This study explored the effects of PbO NP acute and subchronic exposures on mice. Mice were exposed to 4.05 x 10^6 PbO NP/cm^3 for 4-72 hours (acute exposure) or 1-11 weeks (subchronic exposure). PbO NP were found in lungs, liver, kidney, and brain after subchronic exposure, with the highest PbO NP content observed in the lungs and kidneys. Morphological alterations were observed and tissue damage were observed in the lungs and liver. Mild pathological

changes were also observed in the kidney and brain.

61. Li, R. *et al.* Atmospheric emissions of Cu and Zn from coal combustion in China: Spatio- temporal distribution, human health effects, and short-term prediction. *Environ Pollut* 229, 724–734 (2017).

This study found that Cu and Zn emissions were significantly associated with mortality and life expectancy through multiple regression analyses. The authors investigated atmospheric Cu and Zn emissions from coal combustion in thirty provinces of China from 1995-2014. Each ton increase in Cu and Zn emissions resulted in 0.001% and 0.0002% increases in mortality, respectively. Each ton increase in emissions resulted in a 0.002-year and 0.001-year decrease in life expectancy for Cu and Zn, respectively. However, the R^2 values for both the mortality and life expectancy models were low (0.446 and 0.357, respectively).

62. Li, X. *et al.* Suppression of PTPN6 exacerbates aluminum oxide nanoparticle-induced COPD-like lesions in mice through activation of STAT pathway. *Part Fibre Toxicol* 14, 53 (2017).

This toxicology study found that aluminum oxide nanoparticles (Al_2O_3 NP) resulted in emphysema and small airway remodeling in mice. Mice were exposed to Al_2O_3 NP for 8 hours per day for 7 consecutive days. Specifically, this study showed that protein tyrosine phosphatase, non-receptor type 6 (PTPN6) inhibition may play a critical role in Al_2O_3 NP induced chronic obstructive pulmonary disease (COPD) lesions in the lungs.

63. Lion, G. N. & Olowoyo, J. O. Possible Sources of Trace Metals in Obese Females Living in Informal Settlements near Industrial Sites around Gauteng, South Africa. *Int J Environ Res Public Health* 20, (2023).

This epidemiology study explored trace metals (Mn, Cr, Ni, Cd, and Pb) in the blood of obese women living in informal settlements around industrial areas. This study included 120 obese

women (BMI ≥ 30) living in Gauteng, South Africa. Given that high metal levels were found at varying sites, results showed that industrial activity may not be the only route of exposure for these trace metals. Instead, lifestyle (presence of smokers in the home, cooking fuel use, etc.) may play an important role. The mean concentrations for Cr, Co, As, and Pb in this study were higher than the limit recommended by the World Health Organization (WHO).

64. Liu, Q., Baumgartner, J. & Schauer, J. J. Source Apportionment of Fine-Particle, Water-Soluble Organic Nitrogen and Its Association with the Inflammatory Potential of Lung Epithelial Cells. *Environ Sci Technol* 53, 9845–9854 (2019).

This study analyzed the chemical composition of PM2.5 collected in Beijing, China to understand these chemicals' attribution to cardiopulmonary disease. Metals were not correlated with proinflammatory cytokines, possibly because of limited binding states with antioxidant enzymes.

65. Lv, J., Zhang, W. & Xu, R. Investigation of radon and heavy metals in Xuanwei and Fuyuan, high lung cancer incidence areas in China. *J Environ Health* 76, 32–38 (2013).

This epidemiology study found that exposure to radon in Xuanwei and Fuyuan (two Chinese counties) had no significant relationship to lung cancer. As and Hg exposure in household coal combustion was not significantly related to abnormal lung cancer incidence. Other carcinogenic metals (beryllium [Be], Pb, Cr, Cd, and Ni) were also found to be at very low levels in other media (soil and water) and therefore were not associated with cancer either.

66. Lyons-Darden, T. *et al.* An Assessment of the Oral and Inhalation Acute Toxicity of Nickel Oxide Nanoparticles in Rats. *Nanomaterials (Basel)* 13, (2023).

This toxicity study found that NiO NP did not exhibit serious acute toxicity in rats. Rats were exposed via oral and inhalation routes to NiOP NP. The median lethal dose (LD_{50} in which 50% mortality is achieved via ingestion) was determined to be >5,000 mg/kg since no rats

died (and no gross abnormalities were observed) following the 14-day observation period for the designed acute oral toxicity experiment. Similarly, the median lethal concentration (LC_{50} in which 50% mortality is achieved via inhalation) was determined to be >5.42 mg/L following four hours of exposure and no deaths to the highest concentration of 5 mg/L.

67. Mainka, A. & Fantke, P. Preschool children health impacts from indoor exposure to PM(2.5) and metals. *Environ Int* 160, 107062 (2022).

This study presents a health impact assessment of metal exposure from $PM_{2.5}$ in indoor air among children in kindergartens in an urban and a rural setting in Poland. Measurements of 11 metals (arsenic, cadmium, chromium, copper, iron, manganese, nickel, lead, antimony, selenium, and zinc) were taken in winter and spring, and used to construct inhalation intake estimates and calculate health effects using (separate) dose-response approaches for PM2.5 and metals. $PM_{2.5}$ impact was 14 μDALY/yr (DALY: disability-adjusted life years; 95% CI: 0.6 - 310 μDALY/yr) and cumulative impact of all metals evaluated was 140 μDALY/yr (0.4 - 8400 μDALY/yr). Hexavalant chromium produced the largest impacts among metals evaluated. Authors conclude that exposure to metals in $PM_{2.5}$ can be a substantial contributor to the overall health impacts of air pollution (cumulative metal risk ~10x greater than $PM_{2.5}$ risk alone), though they note the large uncertainties and emphasize the need for improved dose-response models for metals in $PM_{2.5}$.

68. Manjanatha, M. G. *et al.* Evaluation of cII mutations in lung of male Big Blue mice exposed by inhalation to vanadium pentoxide for up to 8 weeks. *Mutat Res Genet Toxicol Environ Mutagen* 789–790, 46–52 (2015).

This toxicology study evaluates whether gene mutation induced by inhalation of vanadium pentoxide (V_2O_5) is likely to be a key event in the development of observed lung tumors in Big Blue mice. The authors motivate the work by noting that chronic inhalation of V_2O_5 increases incidence of alveolar/bronchiolar tumors in mice at doses of 1 - 4 mg m^{-3}, but literature around

genotoxicity have been mixed. The study exposed mice to particulate aerosols at doses of 0, 0.1, and 1 mg m^{-3} for 4 - 8 weeks and evaluated *cII* mutant frequencies. Mice exposed to the highest concentrations exhibited significant increases in lung weight at the highest aerosol dose, confirming inflammation response from the V_2O_5 particles. However, none of the *cII* mutant frequencies were significantly higher than the corresponding control frequencies, suggesting that mutagenicity is not likely to be an initial key event in the formation of lung tumors from V_2O_5 exposures.

69. McDaniel, D. K. *et al.* Pulmonary Exposure to Magnéli Phase Titanium Suboxides Results in Significant Macrophage Abnormalities and Decreased Lung Function. *Front Immunol* 10, 2714 (2019).

Coal combustion produces large amounts of Magnéli phase titanium suboxides from TiO_2-bearing minerals in coal. Toxicity of these nanoparticles (<1 μm) has been shown *in vitro* with airway epithelial cells and *in vivo* zebrafish. Mice were exposed via intratracheal administration (3 per week, for 6 weeks) to nanoparticulate Ti_6O_{11} at 100 ppm, and local Ti concentrations, lung pathology, and airway mechanics were assessed. Macrophages were found to be the most affected cell type. Macrophages engulfed the particles with their membranes (phagocytosis), but failed to properly eliminate Magnéli phase Ti, resulting in oxidative stress, mitochondrial dysfunction, and cell death, resulting in gene expression profiles consistent with lung injury within 6 weeks of exposure. Results of airway mechanics studies showed that chronic exposure resulted in lung accumulation of Magnéli phase Ti, increasing airway resistance and elastance, and decreasing compliance, consistent with lung stiffening and diminished function.

70. McDermott, S., Salzberg, D. C., Anderson, A. P., Shaw, T. & Lead, J. Systematic Review of Chromium and Nickel Exposure During Pregnancy and Impact on Child Outcomes. *J Toxicol Environ Health A* 78, 1348–1368 (2015).

This study presents a systematic literature review focusing on the impacts of toxic forms of Cr

and Ni during pregnancy and outcomes in newborns and young children. 16 reports satisfying inclusion criteria were scored. Six papers studied birth weight, prematurity, or gestational age; of these, one linked Ni exposure to small size for gestational age, another linked Ni exposure to low birth weight, and four studies found no significant associations. Of six studies examining birth defects, three found no significant associations, one noted an association between Ni and neural tube defects, one showed an association of Ni with structural defects, and one reported a weak effect of Cr exposure on incidence of musculoskeletal defects. In four remaining studies, weak associations were found between hexavalent Cr and neuroblastoma, Ni and autism spectrum disorder, Cr and Ni with DNA damage, and Cr with lymphocyte damage. Among studies rated as good for execution and reliability, there was weak evidence of an association between Ni and autism spectrum disorder and small gestational age, and no significant association between Cr and child outcomes evaluated.

71. McDermott, T. R., Stolz, J. F. & Oremland, R. S. Arsenic and the gastrointestinal tract microbiome. *Environ Microbiol Rep* 12, 136–159 (2020).

This toxicology study investigated the role of particle size in controlling toxicity of manganese oxides (MnO_2) by exposing rats to aerosols in three nanoparticle size classes (mean aerodynamic diameters of 9, 42, and 118 nm) via intratracheal instillation. The neurotoxicity was assessed via spontaneous locomotion measurements and cortical electrical activity, and these behavioral/functional measurements were correlated with Mn concentrations in brain, lung, and blood cells. Body and organ weight changes were measured as general toxicity indices. The study found that the smaller nanoparticles produced greater toxic effects than the largest size. The authors conclude that, in addition to distinguishing toxicity of micron- and nanometer-scale particles, it may be important to further distinguish how toxicity of

particles varies at the nano- (sub-micron) scale.

72. Mirowsky, J. *et al.* The effect of particle size, location and season on the toxicity of urban and rural particulate matter. *Inhal Toxicol* 25, 747–757 (2013).

This study evaluated the *in vitro* and *in vivo* toxicity of coarse and fine particulate matter (PM) collected in the greater New York metropolitan area during two seasons to evaluate seasonal and size-dependent toxicity. Human cell lung endo- and epithelial cells were exposed to PM and analyzed for reactive oxygen species, and mice were exposed and protein levels were measured in lavage fluids. The study found that urban fine PM generated the highest reactive oxygen species response *in vitro* and coarse PM produced the greatest inflammation *in vivo.* Seasonal characterization of PM showed that urban PM had higher Co, Ni, and Zn in the winter coarse fractions, and higher Mg and Cu in the summer. Cd, S, and Se were highest in the fine PM samples and Fe and Sn were highest in the coarse samples. *in vitro* inflammation was most correlated with Cu, Zn, Sb, S, V, and Ni; *in vivo* responses were mixed. The authors conclude that chemical composition of PM may be important to evaluation of toxic responses to PM, but more work is needed.

73. Montiel-Flores, E. *et al.* Alzheimer-like cell death after vanadium pentoxide inhalation. *Heliyon* 7, e07856 (2021).

In this study, the effects of vanadium pentoxide (V_2O_5) inhalation on the hippocampal cytoskeleton (structure of proteins in the cytoplasm of the cell) was evaluated in male rats. Rats (n=12) were given a 1 hour inhalation exposure to 0.02 M V_2O_5, twice per week for either two months or six months. The authors then looked at alterations in pyramidal hippocampal CA1 cytoskeletal structure. Differences in the number of damaged pyramidal cells in the CA1 region were evaluated by one-way ANOVA. Pyramidal hippocampal cell death was significantly greater for rats exposed for 6 months (57%) compared with those exposed for 2 months (25%) and the control. Imaging revealed greater argyrophilic and collapsed somas in V_2O_5-exposed rats than in control rats. Axons

and dendrites also exhibited noticeable morphological differences. The authors conclude that V_2O_5 exposure produces neuronal death in the hippocampus with effects similar to Alzheimer's Disease.

74. More, S. L. *et al.* Review and Evaluation of the Potential Health Effects of Oxidic Nickel Nanoparticles. *Nanomaterials (Basel)* 11, (2021).

This review evaluated literature on the toxicity of nickel oxide and nickel hydroxide nanoparticles. The authors identified 60 studies on inhalation exposure of oxidic nickel particles from 5 to 100 nm (aerodynamic diameter). They found that inflammatory responses in rodents were typically characterized as acute and only displayed chronic effects at high concentration, long duration doses. The authors found no evidence in the reviewed literature linking oxidic nickel exposure to tumor formation events. The authors found some evidence that the toxicity of nickel oxide in the nano- and micro-scale particles may follow a common dose-response relationship if the dose is normalized to surface area. The authors conclude that future experiments on the exposure-dose-response relationship should consider surface area and reactivity of particles in dose metrics.

75. Morgan, J., Bell, R. & Jones, A. L. Endogenous doesn't always mean innocuous: a scoping review of iron toxicity by inhalation. *Journal of Toxicology and Environmental Health, Part B* 23, 107–136 (2020).

This review focused on literature findings related to iron (Fe)-mediated toxicity following inhalation of particulate matter. A broad search yielding 2189 articles and reports published within the preceding 10 years was narrowed to 87 articles. The major findings were that: (1) epidemiological studies showed that iron oxide exposure is correlated with increased incidence of cancer, cardiovascular disease, and respiratory diseases. Inhaled particulate iron induced inflammatory effects *in vitro* and *in vivo*, and was found to be translocated to the brain after inhalation. The review highlights that one potential toxicity mechanism for inhalation of

Fe-bearing PM is generation of reactive oxygen species, which leads to lipid peroxidation and oxidation of DNA and proteins.

76. Ng, C. F. S. *et al.* Associations of chemical composition and sources of PM(2.5) with lung function of severe asthmatic adults in a low air pollution environment of urban Nagasaki, Japan. *Environ Pollut* 252, 599–606 (2019).

Authors studied relationships between the mass, chemical composition, and sources of $PM_{2.5}$ on short-term pulmonary function in 35 adults with severe asthma in a low air pollution environment in urban Nagasaki, Japan. Study participants provided a daily record of morning peak expiratory flow (PEF) in spring 2014 - 2016, and $PM_{2.5}$ filters (n=178) from an air monitoring station were measured for 27 elements. Sulfate (SO_4^{2-}) and $PM_{2.5}$ from oil combustion and traffic were associated with reduced PEF by way of a generalized linear model with generalized estimating equation. An increase in SO_4^{2-} of 3.7 μg/m^3 (corresponding to IQR of measurements) was associated with a decrease of 0.38% in PEF (95% CI: -0.75% to -0.001%). An increase in oil and traffic-sourced $PM_{2.5}$ of 2.64 μg/m^3 (also corresponding to IQR), based on positive matrix factorization-based apportionment, was associated with a PEF decrease of 0.33% (95% CI: -0.62% to -0.002%). Authors conclude that specific constituents of fine particle pollution may be an important driver of ventilatory capacity among adults with severe asthma, though they find no evidence linking total mass and metals to reduced pulmonary function in this low-pollution environment.

77. Ngwa, H. A., Kanthasamy, A., Jin, H., Anantharam, V. & Kanthasamy, A. G. Vanadium exposure induces olfactory dysfunction in an animal model of metal neurotoxicity. *Neurotoxicology* 43, 73–81 (2014).

Authors investigated the neurotoxic effects of vanadium pentoxide (V_2O_5) on the olfactory bulb in mice. To mimic inhalation exposure, a low dose (182 μg) of V_2O_5 was administered to C57 mice intranasally 3 times per week for 1 month, and behavioral, neurochemical, and biochemical

studies were performed. Results showed a significant decrease in olfactory bulb weight, tyrosine hydroxylase levels, dopamine levels (and dopamine's metabolite, 3,4-dihydroxyphenylacetic acid). Results showed a significant increase in astroglia of the glomerular layer of the olfactory bulb in exposed groups relative to controls. These neurochemical changes were associated with impaired locomotion (reduced activity control, distance traveled, and movement time, increased rest time) and ability to perceive odors (reduced time spent sniffing female bedding). Study revealed that subchronic exposure to a low dose of intranasal V_2O_5 induces olfactory dysfunction.

78. Pardo, M., Shafer, M. M., Rudich, A., Schauer, J. J. & Rudich, Y. Single Exposure to near Roadway Particulate Matter Leads to Confined Inflammatory and Defense Responses: Possible Role of Metals. ***Environ Sci Technol*** **49, 8777–8785 (2015).**

The effects of single (sub-clinical) exposure to water-soluble extracts from particulate matter were evaluated in mice. Mice were divided into four treatment groups: (1) particulate matter extract collected from a major European city, (2) particulate matter from a European city which had soluble metals removed by chelation, (3) an artificial metal solution, and (4) control. Each mouse received a single dose of 50 μL of PM water extract corresponding to 10 μg PM2.5. Treatments 1 and 3 produced a 24 hour inflammatory response characterized by increases in cytokines (IL-6 and TNF-α) and broncho-alveolar lavage fluid cells, increases in reactive oxygen species production, and insignificant lipid and protein oxidation adducts in mouse lungs. The responses largely resolved within 48 hours of exposure. Treatment 2 (metals removed by chelation) markedly diminished the pulmonary PM-mediated response, indicating that the metals present in particulate matter are largely responsible for the observed transient local pulmonary inflammation at sub-clinical exposures.

79. Pardo, M., Xu, F., Qiu, X., Zhu, T. & Rudich, Y. Seasonal variations in fine particle composition from Beijing prompt oxidative stress response in mouse lung and liver. ***Sci Total Environ*** **626, 147–155 (2018).**

This study investigated seasonal variation in the composition of $PM_{2.5}$ collected from Beijing, China and the effects of this particulate matter on oxidative stress and inflammation responses in mice. $PM_{2.5}$ samples contained higher concentrations of metals and polycyclic aromatic hydrocarbons (PAHs; an organic compound) in the heating season than the non-heating season. Mice received an intra-tracheal dose of 20 μg of extract in 50 μL volume, each time, for 5 successive exposures. The overall dose is equivalent to 21 micrograms per cubic meter ($\mu g/m^3$) of PM in humans, which is near the lower limit of PM pollution in Asia. Antioxidant response was reduced in the lung and increased in the liver, with a greater response observed to heating season samples. These responses were associated with changes in the Nrf2 transcription factor (a regulator of stress response) and increases in expression of genes related to detoxification of PAHs. In the liver, elevated levels of lipid peroxidation adducts were observed and these correlated with morphological signs of liver cell damage. This study concludes that the toxicity associated with $PM_{2.5}$ likely changes seasonally as the composition of $PM_{2.5}$ changes, and that organs other than the lungs (here, the liver) may be susceptible to toxic effects from $PM_{2.5}$ exposure.

80. Peters, S., Reid, A., Fritschi, L., de Klerk, N. & Musk, A. W. B. Long-term effects of aluminium dust inhalation. *Occup Environ Med* 70, 864–868 (2013).

During the 1950s and 1960s, aluminum dust inhalation was used as a potential prophylaxis against silicosis in underground miners. In this study, researchers investigated the association between aluminum dust inhalation and cardiovascular, cerebrovascular, and Alzheimer's diseases in a cohort of 1,894 Australian male gold miners. The mortality of cohort members was compared with that of the Western Australian male population (1961-2009), and duration of exposure within the cohort was examined by Cox regression. Aluminum dust inhalation was reported for 647 of the 1,894 cohort members. During 42,780 person-years of follow-up, 1,577 deaths were

observed. A non-significant increase in Alzheimer's disease mortality was observed among miners exposed to aluminum dust (standardized mortality ratio=1.38; 95% CI: 0.69 - 2.75) compared to those who were not. An increased risk in cardiovascular disease with increasing duration of aluminum dust inhalation was observed (hazard ratio=1.02; 95% CI: 1.00 -1.04). Additionally, elevated rates of cardiovascular and cerebrovascular death were observed relative to the general Australian male population, but were similar between aluminum dust inhaling and non-dust inhaling miners. No evidence was found for a protective effect of aluminum dust against silicosis.

81. Raaschou-Nielsen, O. *et al.* Particulate matter air pollution components and risk for lung cancer. *Environ Int* 87, 66–73 (2016).

This study assessed associations between particulate matter (PM) components and lung cancer incidence using data from 14 cohort studies in eight European countries. Baseline addresses were geocoded and air pollution was assessed with land-use regression models for eight elements (Cu, Fe, K, Ni, S, Si, V, and Zn) in size fractions of $PM_{2.5}$ and PM_{10}. Cox regression models with adjustment for potential confounders were used in cohort-specific analysis, and random effect models were used for meta-analysis. Cohort members (*n*=245,782) contributed 3,229,220 person–years. 1,878 incident cases of lung cancer were diagnosed during follow-up (mean: 13.1 y). In the meta-analyses, elevated hazard ratios (HRs) for lung cancer were associated with all elements except V, though none was statistically significant. In analyses restricted to participants who did not change residence during follow-up, statistically significant associations were found for $PM_{2.5}$ Cu (HR, 1.25; 95% CI, 1.01–1.53 per 5 ng/m^3), PM_{10} Zn (1.28; 1.02–1.59 per 20 ng/m^3), PM_{10} S (1.58; 1.03–2.44 per 200 ng/m^3), PM_{10} Ni (1.59; 1.12–2.26 per 2 ng/m^3) and PM_{10} K (1.17; 1.02–1.33 per 100 ng/m^3). Authors conclude that PM containing S and Ni may be particularly important for lung cancer risk.

82. Rahman, H. H., Niemann, D. & Munson-McGee, S. H. Environmental exposure to metals

and the risk of high blood pressure: a cross-sectional study from NHANES 2015-2016. ***Environ Sci Pollut Res Int*** **29, 531–542 (2022).**

Study investigated correlation between 19 forms of urinary metal concentrations and high blood pressure (≥130 mm Hg systolic or ≥80 mm Hg diastolic) in the U.S. adult population based on 4,037 adults in the 2015-2016 National Health and Nutrition Examination Survey (NHANES). Urinary arsenous acid, tin, and cesium were associated with increased odds of high blood pressure. Four other types of arsenic and twelve types of urinary metals were not associated with high blood pressure.

83. Rajendran, N., Seagrave, J. C., Plunkett, L. M. & MacGregor, J. A. A comparative assessment of the acute inhalation toxicity of vanadium compounds. ***Inhal Toxicol*** **28, 618–628 (2016).**

This study evaluated the toxicity of micron-scale vanadium particles in different oxidation states in rats and mice given nose-only inhalation exposure. Vanadium is a transition metal which exists in several oxidation states (typically +3, +4, and +5), and the oxidation state affects the reactivity of vanadium compounds with tissues. Among solid aerosols, V_2O_5 was the most acutely toxic. However, $VOSO_4$, which was the only species delivered as an aqueous solution because it is highly water-soluble and hygroscopic, was even more toxic than V_2O_5 in mice but not rats. The authors conclude that interacting characteristics such as species, bioavailability, solubility and oxidation state all impact the toxicity of vanadium compounds.

84. Rosa, M. J. ***et al.*** **Association of recent exposure to ambient metals on fractional exhaled nitric oxide in 9-11 year old inner-city children.** ***Nitric Oxide*** **40, 60–66 (2014).**

This cohort-based health study evaluated fractional exhaled nitric oxide (FENO), a proxy marker of airway inflammation, in 9–11-year-old children (*n*=192). The effects of ambient Ni, V, Zn, and Fe (collected from a local monitoring site over the 9 days preceding evaluation) on FENO and associated inflammation metrics were analyzed using multivariate linear regression.

Associations suggest that these metals lead to airway inflammation in the proximal (Fe) and distal (Ni and V) regions of the lungs, leading to asthma exacerbation. Zn concentrations were not associated with FENO.

85. Saputra, D. *et al.* Short-term manganese inhalation decreases brain dopamine transporter levels without disrupting motor skills in rats. *J Toxicol Sci* 41, 391–402 (2016).

This study investigated the neurotoxic effects of short-term exposure to manganese (Mn) by inhalation. Rats were exposed to $MnCl_2$ aerosol (1.2 μm, 39 mg/m^3) in a nose-only inhalation chamber for 3 weeks. No significant differences were observed between exposed and control rats in a motor coordination test. The Mn-exposed group had significantly higher Mn levels in the lung, blood, olfactory bulb, prefrontal cortex, striatum, and cerebellum compared to the control group. A Mn concentration gradient was observed from the olfactory bulb to the striatum, supporting the idea that Mn is transported to the brain via an olfactory pathway. The Mn-exposed group exhibited signs of mild lung injury and modulation of dopamine transporter expression in the brain.

86. Schmitz, A. E. *et al.* Interaction of curcumin with manganese may compromise metal and neurotransmitter homeostasis in the hippocampus of young mice. *Biol Trace Elem Res* 158, 399–409 (2014).

This toxicology study evaluated the effect of chronic inhalation of a manganese (Mn) mixture [$Mn(OAc)_3$ and $MnCl_2$ (20:40 mM)] over a 14-week period on behavioral and neurochemical endpoints in young mice. The treatment resulted in slight deficits in motor and memory function, resembling early phases of idiopathic Parkinson disease (IPD). Mice given a dietary supplement of curcumin in addition to Mn exposure showed a similar pattern of motor and memory deficits as Mn exposure alone. Furthermore, the combination of curcumin and Mn exposure produced greater increases in Mn and Fe levels in the hippocampus and decreases in serotonin and dopamine levels. This suggests that curcumin

produces synergistic effects with inhaled Mn, which suggests that curcumin may not confer the neuroprotective effects previously shown in some models of idiopathic Parkinson disease.

87. Sherwood, C. L. *et al.* Arsenic compromises conducting airway epithelial barrier properties in primary mouse and immortalized human cell cultures. *PLoS One* 8, e82970 (2013).

Authors evaluated the effects of a 5-day exposure to environmentally-relevant levels of arsenic (<4μM [~300 μg/L (ppb)] as NaAsO2) on airway epithelial barrier function and structure. Main results included evidence that arsenic concentrations (0.9 and 3.9 μM) reduced transepithelial resistance in mouse tracheal epithelial (MTE) cells, which is an indicator of barrier function. Immunofluorescent staining indicated physical changes in MTE cell structure, including altered patterns of localization of transmembrane tight junction proteins compared to untreated controls. This finding was further corroborated through studies showing altered protein expression of select tight junction proteins (Cl-4 and occludin) and altered mRNA levels (Cl-4 and Cl-7) in an immortalized human bronchial cell line (16HBE14o-). Overall findings suggest that environmentally-relevant levels of arsenic alter both the function and the structure of the airway epithelial barrier. Authors conclude that these changes likely contribute to observations of arsenic-induced reductions in immune defense and increases in airway infection.

88. Sobolewski, M. *et al.* The potential involvement of inhaled iron (Fe) in the neurotoxic effects of ultrafine particulate matter air pollution exposure on brain development in mice. *Part Fibre Toxicol* 19, 56 (2022).

Authors evaluated the effects of ultrafine particulate matter on brain development in mice by exposing mice (postnatal days 4-7 and 10-13 for 4 hours per day) to either 1 $\mu g/m^3$ iron oxide (Fe) nanoparticles or 1 $\mu g/m^3$ Fe in conjunction with sulfur dioxide (SO_2; 1.31 mg/m^3, 500 ppb).

Study is motivated by epidemiological evidence that air pollution exposure is tied to various neurodevelopmental disorders including male-biased disorders such as autism spectrum disorder, schizophrenia, and attention deficit hyperactivity disorder. One potential mechanism for such disorders is metal dyshomeostasis. Authors reported altered metal levels in lung and frontal cortex tissues, though effects varied by mouse sex and treatment. In females, reductions in frontal cortex metal levels were observed under Fe-only treatment; in males, increases were observed under Fe + SO_2 treatment. These changes corresponded to changes in brain frontal cortex and striatal neurotransmitter systems at PND14, with Fe+SO_2 changes in glutamatergic and dopaminergic functions that were opposite by sex (+ in males, – in females). In females, increases in glutathione and Il-1a were observed in females only under the Fe+SO_2 treatment. Results highlight the role of chemical mixtures (i.e., Fe alone vs. Fe+SO_2) in mediating toxicity suggest a possible role for Fe to contribute to observed neurotoxicity of ultrafine particles. Male-specific increases in frontal cortex glutamine, glutamate, and GABA and of striatal glutamate and glutamate/GABA under Fe + SO_2 treatment are consistent with persistence UFP-induced excitatory/inhibitory imbalance. Authors note that excitatory/inhibitory imbalance is thought to be a key feature of autism and schizophrenia, both of which are male-biased disorders. Authors conclude that Fe contamination may contribute to features of ambient air pollution, with sex-specific impacts and outcomes potentially tied to neurodevelopmental disorders and neurodegenerative diseases. They note that the number concentration of Fe used in this study far exceeds ambient environmental exposure levels.

89. Tian, T. *et al.* Elevated concentrations of chromium in maternal serum, umbilical cord serum, and cord tissue are associated with an increased risk for orofacial clefts. *Environ Res* 214, 113799 (2022).

This case-control study investigated the association between chromium (Cr) and orofacial clefts (OFCs) in humans. Gestational Cr exposure causes malformations in animal experiments. The

study involved 130 orofacial cleft cases and 260 controls. Maternal serum Cr concentrations among OFC cases were significantly higher than those in controls. The top third of maternal serum concentrations showed significantly greater risk for OFC than the bottom third (odds ratio = 2.13 [1.14-4.05]). Further comparison of Cr concentrations in umbilical cord serum and tissue also showed increases in OFC risk in a dose-dependent, statistically significant manner. Cr concentration in cord tissue was positively associated with indoor coal combustion, suggesting that this may be a source of Cr exposure during pregnancy.

90. Tulinska, J. *et al.* Copper Oxide Nanoparticles Stimulate the Immune Response and Decrease Antioxidant Defense in Mice After Six-Week Inhalation. *Front Immunol* 13, 874253 (2022).

This toxicology study investigated the effects of copper oxide nanoparticles (CuO) on immune/inflammatory response and antioxidant defense in mice exposed to 32.5 μg CuO/m^3 continuously for 6 weeks. The treatment resulted in significant increases in copper content in the lungs and liver of exposed vs. control mice. Copper content in the kidneys, spleen, brain, and blood were similar between exposed and control mice. A variety of immune assays were performed, showing a mix of significant and insignificant differences. Notably, exposure significantly suppressed phagocytic activity of granulocytes and slightly decreased respiratory burst. Exposed mice showed significant decreases in blood concentrations of GSH and GSSG, interpreted as indicating reduced overall antioxidant protection. The authors conclude that sub-chronic inhalation exposure to CuO nanoparticles induces undesired modulation of the immune system.

91. Wang, W.-J. *et al.* Long-term cadmium exposure induces chronic obstructive pulmonary disease- like lung lesions in a mouse model. *Sci Total Environ* 879, 163073 (2023).

This toxicology study investigated the effects of respiratory exposure to cadmium (Cd) on lung physiology and select immunological parameters in adult mice. Mice were exposed to $CdCl_2$ for

4 hours per day for either 10 weeks or 6 months. This study seeks to understand the links between atmospheric fine particle exposure and chronic obstructive pulmonary risk (COPD). Long-term Cd exposed mice showed declines in lung physiology and function, characterized by increases in airway wall thickness, lung weight, and indices of alveolar destruction, as well as deposition of extracellular matrix collagen in the small airway. Furthermore, lung tissues showed signs of inflammatory cell infiltration and a host of cytokines were up-regulated in the lungs of Cd-exposed mice. COPD-like lung lesions were observed in long-term Cd-exposed mice. This study shows that exposure to atmospheric Cd particles produces COPD-like declines in mouse lung function, though it does not test whether similar effects are observed under exposure to aerosols of different compositions.

92. Wang, X. *et al.* Low-level environmental arsenic exposure correlates with unexplained male infertility risk. *Sci Total Environ* 571, 307–313 (2016).

This case-control study evaluates the relationship between low-level general arsenic (As) exposure and unexplained male infertility (UMI) in 101 infertile men with normal semen and 61 fertile men as controls. The authors measured five urinary arsenic species and assessed semen quality based on sperm concentration, volume, motility, and progressive motility. The case group exhibited higher concentrations of 4 As species, total As, and total inorganic As. Urinary levels of pentavalent arsenate were 20x higher in cases than controls. Certain indices from arsenic species were also higher in cases than controls. Logistic regression quantified association between low-level environmental arsenic exposure and UMI risk, demonstrating increasing adjusted odds ratios with each successive quartile of exposure.

93. Xu, Y. *et al.* miR-191 is involved in renal dysfunction in arsenic-exposed populations by regulating inflammatory response caused by arsenic from burning arsenic-contaminated coal. *Hum Exp Toxicol* 39, 37–46 (2020).

This human population-based case study evaluated the effects of arsenic exposure from coal combustion with renal dysfunction in an area with high incidence of arsenic poisoning from coal combustion. A total of 246 villagers were selected by a clustering method, and based on history of arsenic exposure, participants were then stratified into control, low, and high arsenic level groups based on urinary arsenic concentrations. Many control participants were selected from a site approximately 13 km away. The authors measured the expression levels of miR-191 in plasma, cytokines IL-6 and IL-2, and renal dysfunction indicators. The authors find a significant association between miR-191 expression and arsenic-induced renal dysfunction, suggesting that miR-191 is involved in renal dysfunction by regulating inflammatory response.

94. Yang, G. *et al.* Serum Cadmium and Lead, Current Wheeze, and Lung Function in a Nationwide Study of Adults in the United States. *J Allergy Clin Immunol Pract* 7, 2653-2660.e3 (2019).

This epidemiological study examined the relationship between serum concentrations of cadmium (Cd) and lead (Pb) and current wheeze, asthma, and lung function in U.S. adults. The study involved 13,888 adults aged 20 to 79 from the 2007-2012 National Health and Nutrition Examination Survey (NHANES). Multivariable logistic or linear regression was performed first in all patients, and then separately for never/former smokers and current smokers. High levels of serum Cd were significantly associated with current wheeze in both the "all participants" and "current smokers" analyses. The odds ratio between the uppermost and lowermost quartiles was 2.84 [95% CI: 2.07-3.90]. Serum Pb was not significantly associated with current wheeze or current asthma, regardless of smoking status. Serum Cd and Pb were associated with some, but not all indicators of lung function. Overall findings suggest that Cd exposure is associated with increased risk of wheeze and asthma in U.S. adults who currently smoke, and both Cd and Pb exposure have some negative effects on lung function in nonsmokers.

95. Ye, Q. & Kim, J. Effect of olfactory manganese exposure on anxiety-related behavior in a mouse model of iron overload hemochromatosis. *Environ Toxicol Pharmacol* 40, 333–341 (2015).

This toxicology study compared anxiety-related behavior and monoaminergic protein expression between wild-type mice and *Hfe*$^{-/-}$ mice, which are a model for iron overload hemochromatosis. This study builds on a previous study with *Hfe*$^{-/-}$ mice showing that Hfe deficiency altered manganese (Mn) uptake into the brain. Compared with Mn-exposed wild-type mice, *Hfe*$^{-/-}$ mice showed decreased Mn accumulation in the cerebellum. *Hfe*$^{-/-}$ mice also exhibited increased anxiety with decreased exploratory activity and elevated dopamine D1 receptor and norepinephrine transporter in the striatum. The authors conclude that HFE function alters Mn-associated emotional changes and propose that HFE could be a molecular target for addressing affective disorders induced by Mn inhalation.

96. Yuan, G. *et al.* Toxicological assessment of combined lead and cadmium: acute and sub-chronic toxicity study in rats. *Food Chem Toxicol* 65, 260–268 (2014).

This toxicology study investigated the effects of metal mixtures on both acute and sub-chronic toxicity in rats using lead (Pb) and cadmium (Cd). The authors report an LD_{50} level of 2696.54 mg/kg for orally-administered $Pb(NO_3)_2$ and $CdCl_2$. The sub-chronic treatment was shown to cause microcytic hypochomic anemia and damaged the liver and kidney of exposed rats to varying degrees. The authors conclude that Pb and Cd are additive-toxic when it comes to oral acute toxicity.

97. Zhang, L. *et al.* Global impact of atmospheric arsenic on health risk: 2005 to 2015. *Proc Natl Acad Sci U S A* 117, 13975–13982 (2020).

This study developed an improved inventory of global atmospheric arsenic emissions and simulated the atmospheric fate and transport using a global model (GEOS-Chem). In 2005,

highest simulated airborne arsenic concentrations were observed over Chile and eastern China (8.34 and 5.63 ng/m^3, respectively). High arsenic concentrations in Chile reflect strong arsenic emissions from copper smelting, and are stable from 2005 - 2015 (8.34 vs. 8.68 ng/m^3). Arsenic concentrations in China declined between 2005 and 2015 (5.63 to 4.38 ng/m^3), largely reflecting efforts to control fine particulate matter sources from coal-fired power plants and other industrial sources. Increases (2.77 and 4.57 ng/m^3 in 2005 and 2015, respectively) observed in India reflected a dramatic increase in uncontrolled coal combustion in 2015 relative to 2005. Authors performed a global health risk assessment for inhalation exposure of atmospheric arsenic, concluding that 4.09 billion people (95% CI: 2.80 - 4.65 billion) lived with cancer risk above threshold of 1 per million people (10^{-6}) in 2015. Authors further conclude that the combined effect of exposure by both inhalation (from atmosphere) and ingestion (from groundwater) may significantly enhance risks relative to consideration of groundwater intake alone.

98. Zheng, K. *et al.* Kindergarten indoor dust metal(loid) exposure associates with elevated risk of anemia in children. *Sci Total Environ* 851, 158227 (2022).

This cross-sectional survey study investigated the relationship between blood hemoglobin levels and exposure to 11 metal(loid)s in 2165 children from 25 kindergartens in Shandong Province, China. Studies have shown that heavy metals, particularly lead (Pb) are associated with abnormal red blood cell function and decreased hemoglobin levels, and increased risk of anemia. This study assessed connections between environmental exposure to metals and hemoglobin. 351 (16%) of the children studied met the WHO criteria for anemia. Exposure was calculated by measuring the concentrations of metals in indoor dust samples collected from the kindergartens and calculating a daily exposure dose. Using multiple linear regression and logistic regression, the authors found that each quartile increase in Cd inhalation exposure, hemoglobin levels decreased by 2.7 g/L (95% CI: -4.1 to -1.4), and the risk of anemia

increased 1.6-fold. Mn ingestion was also associated with increased odds of anemia. Cluster analysis suggested that children with greater metal exposure in the school environment tended to have lower hemoglobin levels and higher prevalence of anemia, but the results were not statistically significant.