# Association of Environmental Pollutants Exposure with Pulmonary Fibrosis: A Mini Review of Molecular Mechanism Mediated

**Soni Siswanto[1], Bantari W.K. Wardhani[2*]**

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]Faculty of Military Pharmacy, Indonesia Defense University, Bogor, West Java, Indonesia

**ABSTRACT**

Pulmonary fibrosis is a specific form of chronic progressive interstitial lung disease. Deposition of extracellular matrix, mainly collagen, is the pathogenic characteristic of pulmonary fibrosis. Many reports show that environmental pollutants, particularly asbestos, silica, mercury, cadmium, and benzo(a)pyrene, are contributed in the etiology of lung injury and a risk factor in the development of idiopathic pulmonary fibrosis (IPF) in humans. Based on its physicochemical properties, environmental pollutant-induced pulmonary fibrosis can be developed after a particular type or dose of exposure. To date, some studies have focused on variant pollutants that are induced. However, the molecular mechanism of various pollutants to cause lung injury, which leads to pulmonary fibrosis, remained unexplored. Hence, this narrative review articles describe its molecular mechanism in generating pulmonary fibrosis comprehensively. It is helpful to portray the IPF pathogenesis and its drug discovery and development. Collectively, this article also revealed animal models which can be useful for IPF drug development research.

*Keywords: idiopathic pulmonary fibrosis; animal models; lung disease; drug discovery; drug development*

*corresponding author
Email : bantariwisynu@gmail.com*

## INTRODUCTION

Pulmonary fibrosis is a form of interstitial lung disease characterized by chronic, progressive, and fibrosing lung (Raghu et al., 2018). In lung function assessment, pulmonary fibrosis is characterized by reduction of vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1) (Janssens & van Bleyenbergh, 2020). The pathogenic characteristic of fibrosis is marked by the extracellular matrix, mainly collagen, which is expressed by myofibroblast deposition in the lung interstitial (European Respiratory Society, 2013). As shown in Figure 1, the pathogenesis of pulmonary fibrosis starts with lung injury followed by subsequent pathways that cause profibrotic and proinflammatory imbalance, which drive cellular differentiation, that leads to lung fibrosis (Berngard & Afshar, 2016; Drakopanagiotakis et al., 2018; Meyer et al., 2012; Piersma et al., 2015; Sakai & Tager, 2013; Wick et al., 2013). The etiology of pulmonary fibrosis can be classified as idiopathic and known causal (Raghu et al., 2011, 2018). One known risk factor is environmental pollutants-induced idiopathic pulmonary fibrosis (Raghu et al., 2011, 2018).

Several environmental factors have been described to cause pulmonary fibrosis. Previously, air pollution has been reported to cause several lung diseases, including pulmonary fibrosis (Bala et al., 2021; Harari et al., 2020).

Agricultural workers also develop pulmonary fibrosis due to pesticide exposure (Park et al., 2021). Metal workers are prone to develop pulmonary fibrosis due to metal dust inhalation (Assad et al., 2018). Moreover, several other pollutants such as silica and benzo(a)pyrene also have been reported to induce pulmonary fibrosis (Vetrano et al., 1992; Bo et al., 2020; Byczkowski & Kulkarni, 1990).

This article aims to do a narrative review regarding the association of environmental pollutant exposure, domestic or occupational to pulmonary fibrosis and its molecular mechanism. This article will also describe the animal models' similarity to the clinical feature of pulmonary fibrosis.

### Environmental Pollutant

#### Silica

Occupational and non-occupational silica dust has become a public concern due to its relationship with lung diseases. A wide range of industrial activities has been associated with silica dust pollutants. Silica-based industries such as quartz crushing, agate grinding, ceramics, slate pencil, mining and milling of sandstones, silica flour milling, and granite have been reported to release silica dust. People or workers who work or stay in the vicinity of these industries are affected (Bhagia, 2012).
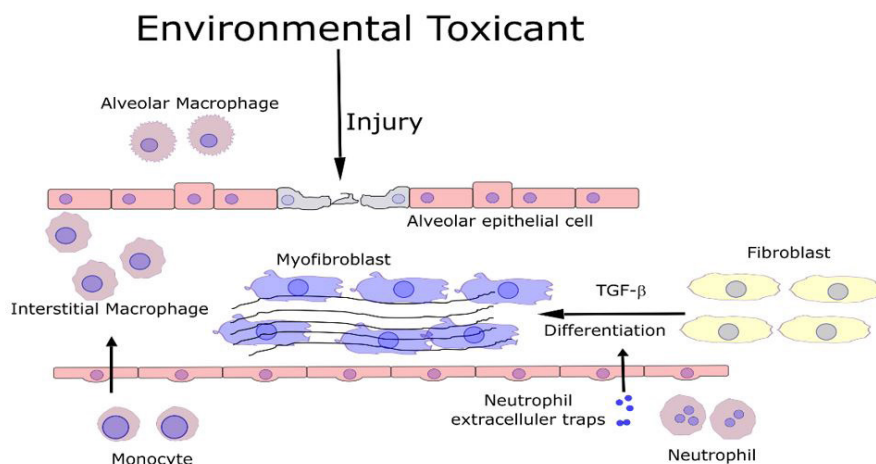
**Figure 1. Pathogenesis of environmental pollutants-induced lung fibrosis**

Silica occurs in two forms, namely amorphous and crystalline silica. Despite its occurrence in nature, amorphous silica is developed synthetically as a functional nanoparticle for therapeutics application (Jafari et al., 2019), and its toxicity has been reviewed previously (Croissant et al., 2020). Crystalline silica inhalation can induce lung fibrosis, usually after long-term exposure (Brown & Rushton, 2005). At the initial stages of silicosis, it is difficult to be detected by chest radiography. But the linear and nodular opacities distributed in both lungs can be found by high-resolution computed tomography scans in both lungs (Song et al., 2013). In addition to the clinical presentation, this finding is an essential tool for the diagnosis of silica-induced pulmonary fibrosis (Cedillo-Pozos et al., 2020).

Several pathogenesis have been proposed regarding the mechanism of silica-induced pulmonary fibrosis. The mechanisms of silica-induced pulmonary fibrosis are DNA damage (Daniel et al., 1993), oxidative stress (Daniel et al., 1995), and epithelial-mesenchymal transition (Guo et al., 2019). In oxidative stress pathogenesis, several oxidative markers, including superoxide dismutase (SOD), gluthathione (GSH), and lipid peroxide, are altered in the rat lung (Yamano et al., 1995). The redox imbalance is reported to be associated with the change of TGFβ1/SMAD signaling (Feng et al., 2019).

Various lung cells, including macrophages, lung epithelial cells, and fibrocytes, have been reported to take part in silica-induced lung fibrosis. Intratracheal instillation of silica induces a cellular change in bronchoalveolar lavage (Feng et al., 2019). Macrophages, one of the cell types that reside in alveolar, regulate several phenotypes, including fibrotic phenotypes (Wynn & Vannella, 2016). In an in vitro study, silica-induced DNA damages and oxidative stress in alveolar macrophage (Zhang et al., 2000). Rat lungs reported developed lung fibrosis 28

days after intratracheal instillation of silicon dioxide. In this study, silica-induced pulmonary fibrosis is regulated by the change of lncRNA expression in the lung (Sai et al., 2019). Change in lncRNA expression can regulate the epithelial-mesenchymal transition of lung epithelial cells that leads to lung fibrosis (Liu Y. et al., 2018). Fibrocyte differentiation to fibroblast also has a role in silica-induced pulmonary fibrosis (Li et al., 2017).

### Asbestos
Asbestos is a mineral compound that naturally occurs in the environment. There are six naturally occurring fibrous magnesium silicate minerals that are referred to as asbestos fibers, namely: chrysotile, crocidolite, amosite tremolite, anthophyllite, and actinolite (Lazarus and Phillip, 2011). The naturally occurring asbestos, which appears as a component of soils or rocks, can be released into the environment because of human activities. The release of asbestos from its deposit to the environment representing a potential risk for human health (Campopiano et al., 2020).

Asbestosis is pneumoconiosis, defined as diffuse interstitial fibrosis of the lung. Detection of retained mineral particles in lung tissue provides valuable information for asbestosis (Gibbs et al., 2014). Differential diagnosis with IPF will be more difficult in the more advanced stages than in the early stages of the disease because it may have the same anamnestic, clinical, functional respiratory, and radiographic features (Stufano et al., 2020).

Asbestosis has been described as a dose-dependent disease (Walters, 2020). In an animal study, prolonged exposure until 56 days (about two months) after asbestos installation induces more severe fibrosis in mice (Yanamala et al., 2018). The exact mechanism of asbestosis is not fully understood. Several mechanisms of asbestos-induced pulmonary fibrosis have been

reported, including oxidative stress (Cui et al., 2019), altered cell's function (Nishimura et al., 2013), and epithelial cells damages which lead to the recruitment of fibrogenic cells (Cheresh et al., 2020), autophagy (Lin et al., 2014).

Seven days after crocidolite installation into mouse lungs, several cells reported an increase in bronchoalveolar lavage (Yanamala et al., 2018). In asbestos-induced pulmonary fibrosis, several cells were also reportedly involved in the development of pulmonary fibrosis. Profibrotic polarization of monocytes-derived macrophages contributes to pulmonary fibrosis mediated by NADPH oxidase 4 (NOX4) (He et al., 2019). Immune cells, such as neutrophils and macrophages, also contribute to the lung's oxidative stress (Funahashi et al., 2015). Lung epithelial cells undergo apoptosis after amosite asbestos perturbation is mediated by endoplasmic reticulum stress (Kamp et al., 2013). Moreover, lung epithelial cells undergo autophagy after chrysotile asbestos treatment through AKT/mTOR and the c-JUN signaling pathway (Lin et al., 2014).

### Mercury

In nature, mercury can exist in different oxidation states. The most abundant one is the oxidized mercuric $Hg^{2+}$ state (O'Connor et al., 2019). Coal combustion is one of the largest mercury emission sources to the air (Liu K. et al., 2018). Among others, mercury can lead to human lung impairment (Pan et al., 2020; Pateda et al., 2018). In the study of oral ingestion of mercury in rats, pulmonary fibrosis is observed in the rat lung. Moreover, airway remodeling was also observed in this study (Naidoo et al., 2019). This lung impairment is similar to the impairment of human lungs after acute inhalation of mercury vapor (Lilis et al., 1985; Lim et al., 1998).

Mercury exposure induced oxidative stress and various lung cells toxicity. Oxidative stress occurs in rat lungs after intraperitoneal treatment of mercury-chloride. In this study, malondialdehyde was increased and glutathione was reduced in rat lungs. In this study, oxidative stress not only occurred in the lung, but also several organs including brain, liver, and kidney (Şener et al., 2007). In another report, the redox imbalance was accompanied by increased neutrophil activation, increased inflammatory cytokines, and increased cell apoptosis in the mercury-induced pulmonary injury in mice (Liu B. et al., 2018). Mercury-induced lung cell toxicity also has been demonstrated in an in vitro study using human lung cell line WI-38 (Ali, 2018). In addition, mercury-induced lung fibroblast apoptosis regulates cell cycle progression (Kim et al., 2021).

### Cadmium

Cadmium is one of the heavy metals and is widely used for electroplating in a battery or in the solar cell (Fiducia et al., 2019). In nature, cadmium is closely related to lead and zinc. This naturally occurring cadmium is released to the environment during mining activity (Hamoudah et al., 2002). Cadmium exposure can be mediated through inhalation of polluted air or through smoking (Ganguly et al., 2018). Acute or chronic cadmium exposure can induce lung impairment in a dose-dependent manner (Ganguly et al., 2018).

In the experimental lung toxicity induced by cadmium, interstitial thickening by cellular infiltration and collagen deposit are observed in rat lungs (Hamoudah et al., 2002; Naidoo et al., 2019). In another study, prolonged inflammation is observed in mice lungs after intraperitoneal injection of cadmium chloride (Kundu et al., 2009). Lung inflammation is mediated by the expression of matrix metalloproteinase-2 (MMP2) (Kundu et al., 2009). The role of oxidative stress in cadmium-induced lung toxicity also has been previously reviewed (Cuypers et al., 2010).

Cadmium was demonstrated to induce lung epithelial cells dead mediated by reactive oxygen species production (Kimura et al., 2019; Kumar et al., 2016). Neutrophils are reported to be involved in promoting lung injury through the formation of neutrophils extracellular traps (Wang et al., 2019). Fibroblast differentiation to myofibroblast was also observed after cadmium treatment (Hu et al., 2017).

### Benzo(a)pyrene

Benzo(a)pyrene (BaP) is one of the most studied polycyclic aromatic hydrocarbons due to its risk to human health (Carrell et al., 1997; Reizer et al., 2019). The formation of BaP is caused by incomplete combustion from both nature and human activity (Reizer et al., 2019). In the atmosphere, BaP can be bound to particulate matter (PM) and inhaled into the lung (Majewski & Piotrowski, 2020). The volatile organic compound such as BaP association with several health problems in humans, including pulmonary fibrosis, has been described in a previous review (Bala et al., 2021).

Animal studies of lung fibrosis induced by BaP also have been demonstrated. Collagen deposition, redox imbalance, and increased expression of inflammatory markers were observed in rat lungs after oral treatment of BaP (Alzohairy et al., 2021). Oxidative stress and collagen deposition were also observed in the mice's lungs (Barnwal et al., 2018). Another report demonstrated that collagen deposition in the lung of mice treated with BaP and in mice treated with bleomycin is similar (Huang et al., 2020).

**Table 1. Route of exposure of environmental pollutants in experimental animal**

| Pollutants | Route of Exposure | Reference |
|---|---|---|
| Silica | Intratracheal instillation | (Feng et al., 2019) |
| Asbestos | Intratracheal instillation | (Yanamala et al., 2018) |
| Mercury | Peroral, intraperitoneal | (Naidoo et al., 2019; Liu B. et al., 2018) |
| Cadmium | Peroral, intraperitoneal | (Naidoo et al., 2019; Kundu et al., 2009) |
| Benzo(a)pyrene | Peroral | (Barnwal et al., 2018) |

Several lung cells were reported to play a role in BaP-induced lung fibrosis, such as fibroblast, immune cells, and epithelial cells (Azari et al., 2019; Chen et al., 2005; Suzuki et al., 2020). Aryl hydrocarbon receptor (AhR) is a receptor located in the cytoplasm (Shi et al., 2020). This receptor-mediated lung epithelial cell reprogramming (Ye et al., 2021). Activation of epithelial-mesenchymal transition of lung epithelial cells was reported dependent on p21 (Hýžďalová et al., 2021).

**Animal Model for Drug Development of Pulmonary Fibrosis**

The concern of environmental pollution is growing continuously because of more evidence in the association with poor health conditions in humans. Environmental pollutants increase alongside human activities, which depend on various natural resources. Those pollutants increase the exposure risk to humans, and some may induce serious health problems. Lung injury that leads to lung fibrosis in humans is induced mainly through the inhalation of environmental pollutants. Many studies have been conducted on the association of environmental pollutants with human lung fibrosis.

The experimental animal model is necessary to confirm the association of environmental pollutants and lung fibrosis and for developing drugs. The lung exposure to environmental pollutants is not necessarily through inhalation. Oral exposure to particulate pollutants leads to lung fibrosis in animal experiments. The exposures of environmental pollutants to animals described in this article are summaries in Table 1. The different exposure routes can give the option for researchers to use animal models of lung fibrosis.

**DISCUSSION**

There are several lung cells that play a role in the development of environmental pollutants-induced lung fibrosis. Several immune cells, such as neutrophils and macrophages, mediated inflammatory response. Persistent inflammatory response leads to lung fibrosis (Suzuki et al., 2020). M2 macrophages are dominating lung alveolar in IPF. It is altered by interleukin-4, interleukin-13, transforming growth factor (TGF-β), and interleukin-10 (Yanagihara et al., 2019). Depleting alveolar macrophages using clodronate also led to less fibrosis (Murray et al., 2011). Moreover, macrophages depletion increases epithelial cells proliferation and increases lung function (Hung et al., 2018).

Except for the pollutants here, the IPF can be triggered by cigarette use, drinking habits, and pathogenic infections that cause recurrent and long-lasting (chronic) lung injury. In our best knowledge, it is difficult to differentiate the mechanism of IPF based on the cause. However, Tao et al (2019) has been shown that inhalation of cadmium in different doses can affect the lung microenvironmental lung thereby changing the balance of lung microbiota.

Environmental dust pollutants such as cadmium, silica, asbestos, and BaP induced repeated lung injury chronically. Simultaneously, it induced activation of macrophage in innate immunity response in the alveolus, as well as redox imbalance in alveolar. These conditions generate enhancement of TGF-beta secretion. Further, it augments autocrine and paracrine pro-fibrogenic signaling pathways. As a result, recruitment and proliferation of fibroblast increases, followed by differentiation and proliferation of myofibroblast. It is due to secretion and accumulation of excessive extracellular matrix, which lead to epithelial mesenchymal transition (EMT) and mediation to IPF (Velagacherla et al., 2022; Raghu and Luca, 2017).

Further, collagen deposition is the main characteristic of lung fibrosis. Apparently, fibrocytes-derived collagen does not contribute to lung fibrosis (Kleaveland et al., 2014). The generation of myofibroblast is crucial in the development of pulmonary fibrosis. In addition to fibroblasts, pericytes contribute to myofibroblast differentiation in the lungs (Rahaman et al., 2014)

In IPF, alveolar becomes stiff and loses its elasticity (Glass et al., 2019). Naturally, individu with IPF become harder to breathe. Other symptoms are chronic cough, fatigue, weight loss, and feeling uncomforted in the chest (Raghu et al., 2017). These symptoms usually occur 2 years before IPF is successfully diagnosed by physicians (Glass et al., 2019; Raghu and Luca, 2017).

Treatment of IPF is aimed to refrain the progression, maintain the quality of life, and prolong patient's survival. Pharmacological intervention was limited to nintedanib and pirfenidone as antifibrotic agents (Pleasants and Tighe, 2019). In addition, Raghu and Luca (2017) mentioned symptom management burdensome and oxygen therapy to overcome shortness of breathing. It also classified others as acid suppressive therapy palliative care, management of comorbidities, pulmonary rehabilitation, vaccination for prevention of respiratory infection, as well as patient education and psycho-emotional support (Arya et al., 2018; Raghu and Luca, 2017).

Nintedanib and pirfenidone are FDA approved and strongly recommended for inhibiting progression of fibrosis (Raghu and Luca, 2017). Nintedanib is well known as a tyrosine kinases inhibitor for fibroblast growth factor receptor, platelet-derived growth factor receptor, and vascular endothelial growth factor receptor. It disrupts proliferation, migration, and differentiation of fibroblast, at once suppressing the secretion of extracellular matrix components in lung fibrosis (Wollin et al., 2015). While the mechanism of pirfenidone is not fully revealed. However, pirfenidone has been promising to inhibit proliferation and differentiation of fibroblast, at one attenuated synthesis collagen in animal lung fibrosis model (Ahluwalia et al., 2014).

The standard for management therapy in IPF patients has been growing rapidly recently along with the increasing incidence of patients. The further research in treatment progresses to gain longer life expectancy and greater quality of life. Both approved FDA drugs for IPF can slow the progression but not ultimately stop and refine the lung fibrosis. The future research might be targeted extracellular matrix deposition and immune response modulation using environmental pollutants as an idiopathic lung fibrosis inducer to generate the in vivo or in vitro models.

**CONCLUSION**

Environmental pollutants are risk factors in the incidence of IPF. To date, IPF is one of the lung diseases that has a low survival rate. Therefore, the environmental pollutants can be used to induce lung fibrosis in animals in a drug development process with the characteristic of the model being robust inflammation followed by fibrosis.

**REFERENCES**

Ahluwalia, N., Shea, B. S., Tager, A. M. (2014). New therapeutic targets in idiopathic pulmonary fibrosis. *American Journal of Respiratory and Critical Care Medicine*, *190(8)*, 867-78.

Aryal, S., Nathan, S. D. (2018). An update on emerging drugs for the treatment of idiopathic pulmonary fibrosis. *Expert Opinion on Emerging Drugs, 23*(2):159-172. https://doi.org/10.1080/14728214.2018.1471465

Ali, H. M. (2018). Mitigative role of garlic and vitamin E against cytotoxic, genotoxic, and apoptotic effects of lead acetate and mercury chloride on WI-38 cells. *Pharmacological Reports*, *70*(4), 804–811. https://doi.org/10.1016/j.pharep.2018.02.009

Alzohairy, M. A., Khan, A. A., Alsahli, M. A., Almatroodi, S. A., & Rahmani, A. H. (2021). Protective Effects of Thymoquinone, an Active Compound of *Nigella sativa*, on Rats with Benzo ( a ) pyrene -Induced and Inflammation. *Molecules*, *26*, 3218.

Assad, N., Sood, A., Campen, M. J., & Zychowski, K. E. (2018). Metal-Induced pulmonary fibrosis. *Current Environmental Health Reports*, *5*, 486–498.

Azari, M. R., Mohammadian, Y., Peirovi, H., Omidi, M., Khodagholi, F., Pourahmad, J., Mehrabi, Y., & Rafieepour, A. (2019). Antagonistic effect of co-exposure to short-multiwalled carbon nanotubes and benzo[a]pyrene in human lung cells (A549). *Toxicology and Industrial Health*, *35*(6), 445–456. https://doi.org/10.1177/0748233719854570

Bala, G. P., Rajnoveanu, R. M., Tudorache, E., Motisan, R., & Oancea, C. (2021). Air pollution exposure — the (in) visible risk factor for respiratory diseases. *Environmental Science and Pollution Research*, *28*, 19615–19628.

Barnwal, P., Vafa, A., Afzal, S. M., Shahid, A., Hasan, S. K., Alpashree, & Sultana, S. (2018). Benzo(a) pyrene induces lung toxicity and inflammation in mice: prevention by carvacrol. *Human and Experimental Toxicology*, *37*(7), 752–761. https://doi.org/10.1177/0960327117735572

Berngard, S. C., & Afshar, K. (2016). Idiopathic pulmonary fibrosis: Past, present, future-a review from Talmadge King's ATS 2016 presentation. *Journal of Thoracic Disease*, *8*(7), S559–S561. https://doi.org/10.21037/jtd.2016.07.31

Bhagia, L. (2012). Non-occupational exposure to silica dust. *Indian Journal of Occupational and Environmental Medicine*, *16*(3), 95–100. https://doi.org/10.4103/0019-5278.111744

Bo, C., Geng, X., Zhang, J., Sai, L., Zhang, Y., Yu, G., Zhang, Z., Liu, K., Du, Z., Peng, C., Jia, Q., & Shao, H. (2020). Comparative proteomic analysis of silica-

induced pulmonary fibrosis in rats based on tandem mass tag (TMT) quantitation technology. *PLoS ONE*, *15*(10 October), 1–15. https://doi.org/10.1371/journal.pone.0241310

Brown, T. P., & Rushton, L. (2005). Mortality in the UK industrial silica sand industry: 2. A retrospective cohort study. *Occupational and Environmental Medicine*, *62*(7), 446–452. https://doi.org/10.1136/oem.2004.017731

Byczkowski, J. Z., & Kulkarni, A. P. (1990). Lipid peroxidation and benzo(a)pyrene derivative co-oxygenation by environmental pollutants. *Bulletin of Environmental Contamination and Toxicology*, *45*(5), 633–640. https://doi.org/10.1007/BF01700979

Campopiano, A., Cannizzaro, A., Olori, A., Angelosanto, F., Rosaria, M., Sinopoli, F., Maria, B., Casalinuovo, F., & Iavicoli, S. (2020). Environmental contamination by naturally occurring asbestos (NOA): Analysis of sentinel animal lung tissue Antonella. *Science of the Total Environment*, *745*, 140990. https://doi.org/10.1016/j.scitotenv.2020.140990

Carrell, C. J., Carrell, T. G., Carrell, H. L., Prout, K., & Glusker, J. P. (1997). Benzo[a]pyrene and its analogues: Structural studies of molecular strain. *Carcinogenesis*, *18*(2), 415–422. https://doi.org/10.1093/carcin/18.2.415

Cedillo-Pozos, A., Ternovoy, S. K., & Roldan-Valadez, E. (2020). Imaging methods used in the assessment of environmental disease networks: A brief review for clinicians. *Insights into Imaging*, *11*(1). https://doi.org/10.1186/s13244-019-0814-7

Chen, J. H., Chou, F. P., Lin, H. H., & Wang, C. J. (2005). Gaseous nitrogen oxide repressed benzo[a]pyrene-induced human lung fibroblast cell apoptosis via inhibiting JNK1 signals. *Archives of Toxicology*, *79*(12), 694–704. https://doi.org/10.1007/s00204-005-0001-0

Cheresh, P., Kim, S. J., Huang, L. S., Watanabe, S., Joshi, N., Williams, K. J. N., Chi, M., Lu, Z., Harijith, A., Yeldandi, A., Lam, A. P., Gottardi, C., Misharin, A. V., Budinger, G. R. S., Natarajan, V., & Kamp, D. W. (2020). The sphingosine kinase 1 inhibitor, pf543, mitigates pulmonary fibrosis by reducing lung epithelial cell mtDNA damage and recruitment of fibrogenic monocytes. *International Journal of Molecular Sciences*, *21*(16), 1–17. https://doi.org/10.3390/ijms21165595

Croissant, J. G., Butler, K. S., Zink, J. I., & Brinker, C. J. (2020). Synthetic amorphous silica nanoparticles: toxicity, biomedical and environmental implications. *Nature Reviews Materials*, *5*(12), 886–909. https://doi.org/10.1038/s41578-020-0230-0

Cui, Y., Zha, Y., Li, T., Bai, J., Tang, L., Deng, J., He, R., Dong, F., & Zhang, Q. (2019). Oxidative effects of lungs in Wistar rats caused by long-term exposure to four kinds of China representative chrysotile. *Environmental Science and Pollution Research*, *26*(18), 18708–18718. https://doi.org/10.1007/s11356-019-04978-6

Cuypers, A., Plusquin, M., Remans, T., Jozefczak, M., Keunen, E., Gielen, H., Opdenakker, K., Nair, A. R., Munters, E., Artois, T. J., Nawrot, T., Vangronsveld, J., & Smeets, K. (2010). Cadmium stress: An oxidative challenge. *BioMetals*, *23*(5), 927–940. https://doi.org/10.1007/s10534-010-9329-x

Daniel, L. N., Mao, Y., & Saffiotti, U. (1993). Oxidative DNA damage by crystalline silica. *Free Radical Biology and Medicine*, *14*, 463–472.

Daniel, L. N., Mao, Y., Wang, T. C., Markey, C. J., Markey, S. P., Shi, X., & Saffiotti, U. (1995). DNA strand breakage, thymine glycol production, and hydroxyl radical generation induced by different samples of crystalline silica in vitro. *Environmental Research*, *71*, 60–73.

Drakopanagiotakis, F., Wujak, L., Wygrecka, M., & Markart, P. (2018). Biomarkers in idiopathic pulmonary fibrosis. *Matrix Biology*, *68–69*, 404–421. https://doi.org/10.1016/j.matbio.2018.01.023

European Respiratory Society. (2013). Interstitial lung diseases. In G. J. Gibson, R. Loddenkemper, Y. Sibille, & B. Lundbäck (Eds.), *The European Lung White Book* (pp. 256–269). https://doi.org/10.1183/2312508X.10003015

Feng, F., Cheng, P., Zhang, H., Li, N., Qi, Y., Wang, H., Wang, Y., & Wang, W. (2019). The protective role of tanshinone IIA in silicosis rat model via TGF-β1/smad signaling suppression, NOX4 inhibition and Nrf2/ARE signaling activation. *Drug Design, Development and Therapy*, *13*, 4275–4290. https://doi.org/10.2147/DDDT.S230572

Fiducia, T. A. M., Mendis, B. G., Li, K., Grovenor, C. R. M., Munshi, A. H., Barth, K., Sampath, W. S., Wright, L. D., Abbas, A., Bowers, J. W., & Walls, J. M. (2019). Understanding the role of selenium in defect passivation for highly efficient selenium-alloyed cadmium telluride solar cells. *Nature Energy*, *4*(6), 504–511. https://doi.org/10.1038/s41560-019-0389-z

Funahashi, S., Okazaki, Y., Ito, D., Asakawa, A., Nagai, H., Tajima, M., & Toyokuni, S. (2015). Asbestos and multi-walled carbon nanotubes generate distinct oxidative responses in inflammatory cells. *Journal of Clinical Biochemistry and Nutrition*, *56*(2), 111–117. https://doi.org/10.3164/jcbn.14-92

Glass, D.S., Grossfeld, D., Renna, H.A., Agarwala, P., Spiegler, P., Kasselman, L.J., DeLeon, J., Reis, A.B. (2020). Idiopathic pulmonary fibrosis: molecular mechanisms and potential treatment approaches. *Respiratory Investigation*, *58(2)*. https://doi.org/10.1016/j.resinv.2020.04.002

Ganguly, K., Levänen, B., Palmberg, L., Åkesson, A., & Lindén, A. (2018). Cadmium in tobacco smokers: A neglected link to lung disease?. *European Respiratory Review*, *27*(147), 1–8. https://doi.org/10.1183/16000617.0122-2017

Gibbs, A. R., Attanoos, R., Popper, H. H., & Corrin, B. (2014). *Pathology of Asbestosis — An Update of the Diagnostic Criteria*. *May*. https://doi.org/10.1043/1543-2165-134.3.462

Guo, J., Yang, Z., Jia, Q., Bo, C., Shao, H., & Zhang, Z. (2019). Pirfenidone inhibits epithelial-mesenchymal transition and pulmonary fibrosis in the rat silicosis model. *Toxicology Letters*, *300*(October 2018), 59–66. https://doi.org/10.1016/j.toxlet.2018.10.019

Hamoudah, S. Y. ., El Naggar, S. I., & H.H, H. (2002). Histopathological and biochemical evaluation of the pulmonary toxicity of cadmium chloride and thiocarbamate. *The Egyptian Journal of Hospital Medicine*, *7*(1), 28–40. https://doi.org/10.21608/ejhm.2002.18818

Harari, S., Raghu, G., Caminati, A., Cruciani, M., Franchini, M., & Mannucci, P. (2020). Fibrotic interstitial lung diseases and air pollution: A systematic literature review. *European Respiratory Review*, *29*(157), 1–8. https://doi.org/10.1183/16000617.0093-2020

He, C., Larson-Casey, J. L., Davis, D., Hanumanthu, V. S., Longhini, A. L. F., Thannickal, V. J., Gu, L., & Brent Carter, A. (2019). NOX4 modulates macrophage phenotype and mitochondrial biogenesis in asbestosis. *JCI Insight*, *4*(16). https://doi.org/10.1172/jci.insight.126551

Hu, X., Fernandes, J., Jones, D. P., & Go, Y. M. (2017). Cadmium stimulates myofibroblast differentiation and mouse lung fibrosis. *Toxicology*, *383*(November 2016), 50–56. https://doi.org/10.1016/j.tox.2017.03.018

Huang, Z., Wang, S., Liu, Y., Fan, L., Zeng, Y., Han, H., Zhang, H., Yu, X., Zhang, Y., Huang, D., Wu, Y., Jiang, W., Zhu, P., Zhu, X., & Yi, X. (2020). GPRC5A reduction contributes to pollutant benzo[a]pyrene injury via aggravating murine fibrosis, leading to poor prognosis of IIP patients. *Science of the Total Environment*, *739*(389), 139923. https://doi.org/10.1016/j.scitotenv.2020.139923

Hung, L. Y., Sen, D., Oniskey, T. K., Katzen, J., Cohen, N. A., Vaughan, A. E., Nieves, W., Urisman, A., Beers, M. F., Krummel, M. F., & Herbert, D. B. R. (2018). Macrophages promote epithelial proliferation following infectious and non-infectious lung injury through a Trefoil factor 2-dependent mechanism. *Mucosal Immunology*, *12*(1), 64-76. https://doi.org/10.1038/s41385-018-0096-2

Hýžďalová, M., Procházková, J., Strapáčová, S., Svržková, L., Vacek, O., Fedr, R., Andrysík, Z., Hrubá, E., Líbalová, H., Kléma, J., Topinka, J., Mašek, J., Souček, K., Vondráček, J., & Machala, M. (2021). A prolonged exposure of human lung carcinoma epithelial cells to benzo[a]pyrene induces p21-dependent epithelial-to-mesenchymal transition (EMT)-like phenotype. *Chemosphere*, *263*. https://doi.org/10.1016/j.chemosphere.2020.128126

Jafari, S., Derakhshankhah, H., Alaei, L., Fattahi, A., Varnamkhasti, B. S., & Saboury, A. A. (2019). Mesoporous silica nanoparticles for therapeutic/diagnostic applications. *Biomedicine and Pharmacotherapy*, *109*(August 2018), 1100–1111. https://doi.org/10.1016/j.biopha.2018.10.167

Janssens, W., & van Bleyenbergh, P. (2020). Lung function in asthma, chronic obstructive pulmonary disease and lung fibrosis. In R. L. Maynard, S. J. Pearce, B. Nemery, P. D. Wagner, & B. G. Cooper (Eds.), *Cotes' Lung Function* (7th ed., pp. 681–696). Wiley Blackwell.

Kamp, D. W., Liu, G., Cheresh, P., Kim, S. J., Mueller, A., Lam, A. P., Trejo, H., Williams, D., Tulasiram, S., Baker, M., Ridge, K., Chandel, N. S., & Beri, R. (2013). Asbestos-induced alveolar epithelial cell apoptosis: The role of endoplasmic reticulum stress response. *American Journal of Respiratory Cell and Molecular Biology*, *49*(6), 892–901. https://doi.org/10.1165/rcmb.2013-0053OC

Kim, J. Y., An, M. J., Shin, G. S., Lee, H. M., Kim, M. J., Kim, C. H., & Kim, J. W. (2021). Mercury chloride but not lead acetate causes apoptotic cell death in human lung fibroblast mrc5 cells via regulation of cell cycle progression. *International Journal of Molecular Sciences*, *22*(5), 1–14. https://doi.org/10.3390/ijms22052494

Kimura, K., Nakano, Y., Sugizaki, T., Shimoda, M., Kobayashi, N., Kawahara, M., & Tanaka, K. I. (2019). Protective effect of polaprezinc on cadmium-induced injury of lung epithelium. *Metallomics*, *11*(7), 1310–1320. https://doi.org/10.1039/c9mt00060g

Kleaveland, K. R., Velikoff, M., Yang, J., Agarwal, M., Rippe, R. A., Moore, B. B., & Kim, K. K. (2014). Fibrocytes Are Not an Essential Source of

Type I Collagen during Lung Fibrosis. *The Journal of Immunology*, *193*(10), 5229–5239. https://doi.org/10.4049/jimmunol.1400753

Kumar, K. M. K., Kumar, M. N., Patil, R. H., Nagesh, R., Hegde, S. M., Kavya, K., Babu, R. L., Ramesh, G. T., & Sharma, S. C. (2016). Cadmium induces oxidative stress and apoptosis in lung epithelial cells. In *Toxicology Mechanisms and Methods* (Vol. 26, Issue 9). https://doi.org/10.1080/15376516.2016.1223240

Kundu, S., Sengupta, S., Chatterjee, S., Mitra, S., & Bhattacharyya, A. (2009). Cadmium induces lung inflammation independent of lung cell proliferation: A molecular approach. *Journal of Inflammation*, *6*, 1–15. https://doi.org/10.1186/1476-9255-6-19

Lazarus, A. A., & Philip, A. (2011). Asbestosis. *Disease-a-Month*, *57*(1), 14–26. https://doi.org/10.1016/j.disamonth.2010.11.004

Li, J., Yao, W., Hou, J. Y., Lin, Z., Bao, L., Chen, H. T., Wang, D., Yue, Z. Z., Li, Y. P., Zhang, M., & Hao, C. F. (2017). Crystalline silica promotes rat fibrocyte differentiation *in vitro*, and fibrocytes participate in silicosis *in vivo*. *Biomedical and Environmental Sciences*, *30*(9), 649–660. https://doi.org/10.3967/bes2017.086

Lilis, R., Miller, A., & Lerman, Y. (1985). Acute mercury poisoning with severe chronic pulmonary Manifestations. *CHEST*, *88*(2), 306–309. https://doi.org/10.1378/chest.88.2.306

Lim, H. E., Shim, J. J., Lee, S. Y., Lee, S. H., Kang, S. Y., Jo, J. Y., In, K. H., Kim, H. G., Yoo, S. H., & Kang, K. H. (1998). Mercury inhalation poisoning and acute lung injury. *The Korean Journal of Internal Medicine*, *13*(2), 127–130.

Lin, Z., Liu, T., Kamp, D. W., Wang, Y., He, H., Zhou, X., Li, D., Yang, L., Zhao, B., & Liu, G. (2014). AKT/mTOR and c-Jun N-terminal kinase signaling pathways are required for chrysotile asbestos-induced autophagy. *Free Radical Biology and Medicine*, *72*, 296–307. https://doi.org/10.1016/j.freeradbiomed.2014.04.004

Liu, B., Yu, H., Baiyun, R., Lu, J., Li, S., Bing, Q., Zhang, X., & Zhang, Z. (2018). Protective effects of dietary luteolin against mercuric chloride-induced lung injury in mice: Involvement of AKT/Nrf2 and NF-κB pathways. *Food and Chemical Toxicology*, *113*(July 2017), 296–302. https://doi.org/10.1016/j.fct.2018.02.003

Liu, K., Wang, S., Wu, Q., Wang, L., Ma, Q., Zhang, L., Li, G., Tian, H., Duan, L., & Hao, J. (2018). A highly resolved mercury emission inventory of Chinese coal-fired power plants. *Environmental Science and Technology*, *52*(4), 2400–2408. https://doi.org/10.1021/acs.est.7b06209

Liu, Y., Li, Y., Xu, Q., Yao, W., Wu, Q., Yuan, J., Yan, W., Xu, T., Ji, X., & Ni, C. (2018). Long non-coding RNA-ATB promotes EMT during silica-induced pulmonary fibrosis by competitively binding miR-200c. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1864*(2), 420–431. https://doi.org/10.1016/j.bbadis.2017.11.003

Majewski, S., & Piotrowski, W. J. (2020). Air pollution—an overlooked risk factor for idiopathic pulmonary fibrosis. *Journal of Clinical Medicine*, *10*(1), 77. https://doi.org/10.3390/jcm10010077

Meyer, K. C., Raghu, G., Baughman, R. P., Brown, K. K., Costabel, U., Du Bois, R. M., Drent, M., Haslam, P. L., Kim, D. S., Nagai, S., Rottoli, P., Saltini, C., Selman, M., Strange, C., & Wood, B. (2012). An official American Thoracic Society clinical practice guideline: The clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. *American Journal of Respiratory and Critical Care Medicine*, *185*(9), 1004–1014. https://doi.org/10.1164/rccm.201202-0320ST

Murray, L. A., Chen, Q., Kramer, M. S., Hesson, D. P., Argentieri, R. L., Peng, X., Gulati, M., Homer, R. J., Russell, T., Van Rooijen, N., Elias, J. A., Hogaboam, C. M., & Herzog, E. L. (2011). TGF-beta driven lung fibrosis is macrophage dependent and blocked by serum amyloid P. *International Journal of Biochemistry and Cell Biology*, *43*(1), 154–162. https://doi.org/10.1016/j.biocel.2010.10.013

Naidoo, S. V. K., Bester, M. J., Arbi, S., Venter, C., Dhanraj, P., & Oberholzer, H. M. (2019). Oral exposure to cadmium and mercury alone and in combination causes damage to the lung tissue of Sprague-Dawley rats. *Environmental Toxicology and Pharmacology*, *69*(March), 86–94. https://doi.org/10.1016/j.etap.2019.03.021

Nishimura, Y., Maeda, M., Kumagai-Takei, N., Lee, S., Matsuzaki, H., Wada, Y., Nishiike-Wada, T., Iguchi, H., & Otsuki, T. (2013). Altered functions of alveolar macrophages and NK cells involved in asbestos-related diseases. *Environmental Health and Preventive Medicine*, *18*(3), 198–204. https://doi.org/10.1007/s12199-013-0333-y

O'Connor, D., Hou, D., Ok, Y. S., Mulder, J., Duan, L., Wu, Q., Wang, S., Tack, F. M. G., & Rinklebe, J. (2019). Mercury speciation, transformation, and transportation in soils, atmospheric flux, and implications for risk management: A critical review. *Environment*

*International*, *126*(November 2018), 747–761. https://doi.org/10.1016/j.envint.2019.03.019

Pan, Z., Guo, Y., Xiang, H., Hui, Y., Ju, H., Xu, S., & Li, L. (2020). Effects of lead, mercury, and cadmium co-exposure on children's pulmonary function. *Biological Trace Element Research*, *194*(1), 115–120. https://doi.org/10.1007/s12011-019-01772-w

Park, Y., Ahn, C., & Kim, T. H. (2021). Occupational and environmental risk factors of idiopathic pulmonary fibrosis: a systematic review and meta-analyses. *Scientific Reports*, *11*(1), 1–10. https://doi.org/10.1038/s41598-021-81591-z

Pateda, S. M., Sakakibara, M., & Sera, K. (2018). Lung function assessment as an early biomonitor of mercury-induced health disorders in artisanal and small-scale gold mining areas in Indonesia. *International Journal of Environmental Research and Public Health*, *15*(11), 14–23. https://doi.org/10.3390/ijerph15112480

Piersma, B., Bank, R. A., & Boersema, M. (2015). Signaling in Fibrosis: TGF-β, WNT, and YAP/TAZ Converge. *Frontiers in Medicine*, *2*(September), 1–14. https://doi.org/10.3389/fmed.2015.00059

Pleasants, R., Tighe RM. (2019). Management of idiopathic pulmonary fibrosis. *Annals of Pharmacotherapy*. 53(12): 1238-48. https://doi.org/10.1177%2F1060028019862497

Raghu, G., Collard, H. R., Egan, J. J., Martinez, F. J., Behr, J., Brown, K. K., Colby, T. V., Cordier, J. F., Flaherty, K. R., Lasky, J. A., Lynch, D. A., Ryu, J. H., Swigris, J. J., Wells, A. U., Ancochea, J., Bouros, D., Carvalho, C., Costabel, U., Ebina, M., … Schünemann, H. J. (2011). An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. *American Journal of Respiratory and Critical Care Medicine*, *183*(6), 788–824. https://doi.org/10.1164/rccm.2009-040GL

Raghu, G., Remy-Jardin, M., Myers, J. L., Richeldi, L., Ryerson, C. J., Lederer, D. J., Behr, J., Cottin, V., Danoff, S. K., Morell, F., Flaherty, K. R., Wells, A., Martinez, F. J., Azuma, A., Bice, T. J., Bouros, D., Brown, K. K., Collard, H. R., Duggal, A., … Wilson, K. C. (2018). Diagnosis of idiopathic pulmonary fibrosis an Official ATS/ERS/JRS/ALAT clinical practice guideline. *American Journal of Respiratory and Critical Care Medicine*, *198*(5), e44–e68. https://doi.org/10.1164/rccm.201807-1255ST

Raghu G, Luca R. (2017). Current approaches to the management of idiopathic pulmonary fibrosis. *Respiratory Medicine*, 129:24-30. http://dx.doi.org/10.1016/j.rmed.2017.05.017

Rahaman, S. O., Tschumperlin, D. J., Mitchell, A., Rahaman, S. O., Grove, L. M., Paruchuri, S., Southern, B. D., Abraham, S., Niese, K. A., Scheraga, R. G., Ghosh, S., Thodeti, C. K., Zhang, D. X., Moran, M. M., Schilling, W. P., Tschumperlin, D. J., & Olman, M. A. (2014). TRPV4 mediates myofibroblast differentiation and pulmonary fibrosis in mice. *Journal of Clinical Investigation*, *124*(12), 5225–5238. https://doi.org/10.1172/JCI75331.that

Reizer, E., Csizmadia, I. G., Palotás, Á. B., Viskolcz, B., & Fiser, B. (2019). Formation mechanism of benzo(a)pyrene: One of the most carcinogenic polycyclic aromatic hydrocarbons (PAH). *Molecules*, *24*(6). https://doi.org/10.3390/molecules24061040

Sai, L., Yu, G., Bo, C., Zhang, Y., Du, Z., Li, C., Zhang, Z., Jia, Q., Shao, H., & Peng, C. (2019). Profiling long non-coding RNA changes in silica-induced pulmonary fibrosis in rat. *Toxicology Letters*, *310*(March), 7–13. https://doi.org/10.1016/j.toxlet.2019.04.003

Sakai, N., & Tager, A. M. (2013). Fibrosis of two: Epithelial cell-fibroblast interactions in pulmonary fibrosis. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1832*(7), 911–921. https://doi.org/10.1016/j.bbadis.2013.03.001

Şener, G., Sehirli, Ö., Tozan, A., Velioğlu-Övunç, A., Gedik, N., & Omurtag, G. Z. (2007). Ginkgo biloba extract protects against mercury(II)-induced oxidative tissue damage in rats. *Food and Chemical Toxicology*, *45*(4), 543–550. https://doi.org/10.1016/j.fct.2006.07.024

Shi, Y., Zeng, Z., Yu, J., Tang, B., Tang, R., & Xiao, R. (2020). The aryl hydrocarbon receptor: An environmental effector in the pathogenesis of fibrosis. *Pharmacological Research*, *160*(August), 105180. https://doi.org/10.1016/j.phrs.2020.105180

Song, J. W., Jeong, Y. J., Kim, K. I., Choi, S. J., Lee, H. K., Lee, K. N., & Manzano, A. C. (2013). Environmental lung diseases: Clinical and imaging findings. *Clinical Radiology*, *68*(3), 310–316. https://doi.org/10.1016/j.crad.2012.07.012

Stufano, A., Scardapane, A., Pia, M., Barbaro, F., Corradi, M., & Lovreglio, P. (2020). Clinical and

radiological criteria for the differential diagnosis between asbestosis and idiopathic pulmonary fibrosis : Application in two cases. *Med Lav*, *112*(2), 115–122. https://doi.org/10.23749/mdl.v112i2.10473

Suzuki, T., Hidaka, T., Kumagai, Y., & Yamamoto, M. (2020). Environmental pollutants and the immune response. *Nature Immunology*, *21*(12), 1486–1495. https://doi.org/10.1038/s41590-020-0802-6

Velagacherla, V., Mehta, C.H., Nayak, Y., Nayak, U.Y. (2022). Molecular pathways and role of epigenetics in the idiopathic pulmonary fibrosis. *Life Sciences*, *291.* https://doi.org/10.1016/j.lfs.2021.120283.

Vetrano, K. M., Morris, J. B., & Hubbard, A. K. (1992). Silica-induced pulmonary inflammation and fibrosis in mice is altered by acute exposure to nitrogen dioxide. *Journal of Toxicology and Environmental Health*, *37*(3), 425–442. https://doi.org/10.1080/15287399209531681

Walters, G. I. (2020). Occupational exposures and idiopathic pulmonary fibrosis. *Current Opinion in Allergy & Clinical Immunology*, *20*(2), 103–111. https://doi.org/10.1097/aci.0000000000000610

Wang, C., Wei, Z., Han, Z., Wang, J., Zhang, X., Wang, Y., Liu, Q., & Yang, Z. (2019). Neutrophil extracellular traps promote cadmium chloride-induced lung injury in mice. *Environmental Pollution*, *254*, 113021. https://doi.org/10.1016/j.envpol.2019.113021

Wick, G., Grundtman, C., Mayerl, C., Wimpissinger, T.-F., Feichtinger, J., Zelger, B., Sgonc, R., & Wolfram, D. (2013). The Immunology of Fibrosis. In *Annual Review of Immunology* (Vol. 31, Issue 1). https://doi.org/10.1146/annurev-immunol-032712-095937

Wollin, L., Wex, E., Pautsch, A., Schnapp, G., Hostettler, K.E., Stowasser, S., Kolb, M. (2015). Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. *European Respiratory Journal,* 45:1434-45. http://doi.org/10.1183/09031936.00174914

Wynn, T. A., & Vannella, K. M. (2016). Macrophages in tissue repair, regeneration, and fibrosis. *Immunity*, *44*(3), 450–462. https://doi.org/10.1016/j.immuni.2016.02.015

Yamano, Y., Kagawa, J., Hanaoka, T., Takahashi, T., Kasai, H., Tsugane, S., & Watanabe, S. (1995). Oxidative DNA damage induced by silica *in vivo*. *Environmental Research*, *69*, 102–107.

Yanagihara, T., Sato, S., Upagupta, C., Kolb, M. (2019). What have we learned from basic science studies on idiopathic pulmonary fibrosis?. *European Respiratory Review,* 28. https://doi.org/10.1183/16000617.0029-2019

Yanamala, N., Kisin, E. R., Gutkin, D. W., Shurin, M. R., Harper, M., & Shvedova, A. A. (2018). Characterization of pulmonary responses in mice to asbestos/asbestiform fibers using gene expression profiles. *Journal of Toxicology and Environmental Health - Part A: Current Issues*, *81*(4), 60–79. https://doi.org/10.1080/15287394.2017.1408201

Ye, G., Gao, H., Zhang, X., Liu, X., Chen, J., Liao, X., Zhang, H., & Huang, Q. (2021). Aryl hydrocarbon receptor mediates benzo[a]pyrene-induced metabolic reprogramming in human lung epithelial BEAS-2B cells. *Science of the Total Environment*, *756*, 144130. https://doi.org/10.1016/j.scitotenv.2020.144130

Zhang, Z., Shen, H. M., Zhang, Q. F., & Ong, C. N. (2000). Involvement of oxidative stress in crystalline silica-induced cytotoxicity and genotoxicity in rat alveolar macrophages. *Environmental Research*, *82*(3), 245–252. https://doi.org/10.1006/enrs.1999.4025