EFFECTS OF AMBIENT AIR POLLUTION ON HUMAN'S RESPIRATORY HEALTH: AN ENVIRONMENTAL HEALTH PERSPECTIVE

By Ngatu Roger Nlandu, MD. PhD.; Associate Professor

Department of Global, School of Medicine and Graduate School of Public Health

International University of Health and Welfare (IUHW). Office: IUHW Narita campus,

Narita 286-8686, Japan. E-mail: doc.rogerngatu@gmail.com

Abstract

Ambient air pollution (AAP) represents a major environmental issue of global concern over the years, with harmful toxicological effects on human health. Globally, it is the number one environmental health risk and is considered a 'silent killer', causing more deaths than other 'big killers' such as HIV/AIDS, Tuberculosis and Malaria. Nowadays, AAP produced by human activities such as industry, mining, mechanized agriculture, petroleum-powered vehicles and electricity-generating power plants, chemical manufacturing companies, etc. are on the rise, threatening the health of populations worldwide. In low and middle-income countries of Asia and Africa in particular, as well as some high-income countries, fuel combustion and biomass burning - which account for approximately 85% of airborne particulate pollution - are major sources of greenhouse gasthat contribute to climate change. Recent reports show that AAP was estimated to cause 4,200,000 premature deaths annually worldwide, mainly due to environmental exposure to small particulate matter (PM_{2.5}, PM₁₀) that cause respiratory diseases, cardiovascular disorders and cancer. In 2007, the World Bank has reported that, in China, AAP was associated with 20,000,000 cases of respiratory diseases and over 300,000 deaths annually. Major outdoor and indoor air pollutants (in both the living and working environments) include particulate matter (PM), carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), polycycic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs). Obviously, the respiratory system is one of the principal targets of air pollutants. Several studies have shown associations between environmental and/or occupational exposure to air pollutants and diseases of the respiratory tract, including asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. Improving the quality of ambient air may help to reduce morbidity due to AAPcaused noncommunicable diseases (NCDs), including respiratory diseases, and avert many cases of NCD-associated deaths.

***Keywords**: Ambient air pollution; Environmental exposure; Pollutant; Respiratory health.

1. General introduction

1.1. Ambient Air Pollution: A Major Environmental Health Risk

Ambient air pollution (AAP) represents a major environmental issue of global concern, with harmful toxicological effects on human health. It is one of the major killers of our age and affects the health of people of all ages, including babies, children, young adults, adults and the elderly. Globally, AAP is the number one environmental health risk to health according to the World Health Organization (WHO); it is considered a 'silent killer', causing more deaths than other 'big killers' such as HIV/AIDS, Tuberculosis and Malaria (Pruss-Ustun et al 2016; Landrigan, 2017).

Synergies between AAP and climate change are reported to increase the harm to children's health due to exposure to increased amounts of environmental pollutants (Perera, 2018). In low and middle-income countries of Asia and Africa, as well as in some high-income countries, fuel combustion and biomass burning - which account for approximately 85% of airborne particulate pollution – are major source of greenhouse gas that contribute to climate change. Nowadays, though the nature air pollution has been changing due to the decline in indoor pollution (thanks to the progress made in replacing the use of biomass as fuels for heating and cooking) by renewable sources of energy, increased concentrations of air pollutants has been observed due to the expansion of mega cities and other human activities. Worldwide, there are human activities that contribute to AAP: the mining industry, petroleum-powered vehicles that produce chemicals during road traffic such diesel exhausted particles (DEP), mechanized agriculture with proliferation of pesticides, chemical manufacturing companies. They are on the rise, threatening the health of populations ('Global Burden of Disease Risk Factors collaborators 2015', 2016; Landrigan, 2017).

1.2. Impact of Ambient Air Pollution in Asia-Pacific and Sub-Saharan Africa regions

1.2.1. AAP in the Asia-Pacific region

AAP is one of major risk factors that contribute to the occurrence of noncommunicable diseases (NCDs), which account for 70% of all deaths occurring worldwide. It is the second leading cause of death from NCDs, after tobacco smoking (WHO, 2019). Recent reports from the World Health organization (WHO, 2018) show that AAP causes 4,200,000 premature deaths annually worldwide, mainly due to environmental exposure to small particulate matter of 2.5 microns or less in diameter (PM_{2.5}), which cause respiratory and cardiovascular diseases, and cancers as well. Furthermore, according to the same reports, AAP is, at least partially, responsible for the increasing rates of Disability Adjusted Life Years (DALYs), especially in South-East Asia.

About 91% of those premature deaths occur in low and middle-income countries, with South-East Asia and Western Pacific countries bearing the greatest burden. In 2007, the World Bank has reported that, in China, AAP was associated with 20,000,000 cases of respiratory diseases and over 300,000 deaths annually. Additionally, the occurrence of outdoor air pollution combined with water pollution cost approximately 100 billion US dollars to the Chinese economy annually (The World Bank, 2007; Marino et al., 2015).

The 'Asian dust', a seasonal dust storm that frequently occurs in winter and spring, is another contributor to AAP in east and south-east Asia, reaching approximately 43 million tons. Usually, it originates from either China or Mongolia and then carry the soil particles to the eastern and southeastern areas towards Taiwan, Japan, Republic of Korea and the Philippines. Moreover, epidemiologic studies have shown evidence of deleterious effects of the dust storm-contained airborne particles on human health, the respiratory health in particular, increasing hospitalization rates and mortality in affected zones (Chen et al., 2004; Bell et al., 2008; Yu et al., 2012). Those studies and others showed significant association between the dust storm occurrence on one hand, and asthma and intra-cerebral hemorrhagic stroke hospital admissions in Taiwanese children.

In Japan, well-known major sources of AAP pollution from 1950's to 1970's have been industrial settings and motorization (Nakao et al., 2019). However, thanks to the rapid

development of new and environment-friendly technologies, as well as the efforts by policymakers and the public administration, there is a decrease in amount of pollutants generated by manufacturing industries and road traffic. Nonetheless, a great concern remains in regard to air pollution associated to Asian dust, which comes from the mainland of East-Asia region. Two recent studies conducted by Shima (2017) and Nakao and colleagues (2019) in sample of adult Japanese people showed that environmental exposure to air pollutants triggered respiratory symptoms in both participants with and without pre-existing chronic respiratory disorders. Furthermore, exposure to air pollutants during episodes of Asian dust was associated with allergic symptoms.

In Korea, a recent systematic review of studies that investigated quantitative associations between air pollutants (PM₁₀, PM_{2.5}, SO₂, NO₂, O₃, CO) and risk of morbidity and mortality among Korean populations showed evidence of causal association with morbidity (Bae and Kwon, 2019).

1.2.2. AAP in Sub-Saharan Africa

Sub-Saharan Africa (SSA) region is said to experience an epidemiological transition characterized by the rapid rise in NCDs - besides infectious diseases - that might be explained by changes in lifestyle, the growing urbanization in Africa and, of course, air pollution. It has resulted in increased prevalence of NCDs, aggravation of pre-existing lung and heart diseases, premature deaths and reduced life expectancy (Katoto et al., 2019). In Africa, major contributors to AAP include informal and formal mining, agriculture, construction and transportation sectors; however, in the scientific literature, not many studies have been reported, especially in relation to the SSA region.

For almost a decade, we have been implementing international collaborative studies that evaluate the health effects of chronic occupational or environmental exposure to dusts in the Democratic Republic of Congo (DRC) (Ngatu et al., 2012; Kabamba et al., 2018). PM_{2.5} concentrations eight times higher or more than exposure limit levels recommended by WHO were found in coltan mining, stone quarry and construction sites during air quality monitoring for respiratory health risk assessment. Higher prevalence of asthma-like symptoms (wheezing, breathlessness) and chronic bronchitis (coughing, sputum, etc.) among construction workers, female stone quarry workers (Congo Environment and Health Research Team, 2019), open mines and underground mines sites, and several cases of Silicosis - a lung fibrotic disease - were diagnosed, with impaired lung function. Similar studies conducted in African copper, cobalt and gold miners in Ghana, South Africa and DRC showed evidence of the toxic effects of mineral dusts on the respiratory system (Bio et al., 2007; Bateman, 2012).

2. Air Quality as Indicator of Sustainable Development

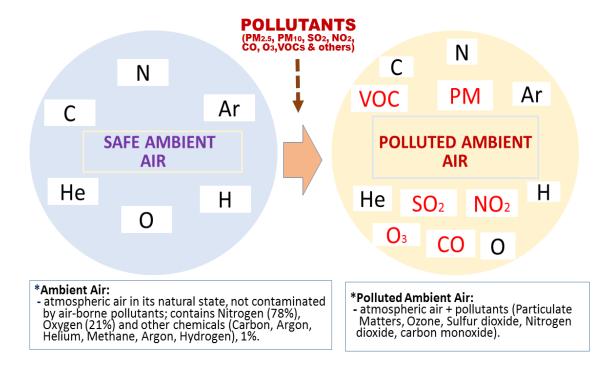


Fig.1- Difference in the composition of safe (unpolluted) and polluted ambient air (source: author)

Sources of air pollution generate pollutants that have a great potential to modify the climate, threatening the lives and well-being of exposed populations. The United Nations' sustainable development goals (SDGs), in particular SDG3 and SDG7, are closely related to the quality of the living environment. Thus, the concern about pollution of ambient air is reflected in SDGs, which implies the necessity for government of countries to ensure good health and well-being of their population (SDG3) and promote access to clean energy (SDG7) that prevent AAP and climate change.

Normally, ambient air is comprised of nitrogen (N), carbon (C), helium (He), hydrogen (H), argon (Ar) and oxygen (O). In circumstances where the atmosphere is contaminated by air pollutants due human activities or natural phenomena such as storm, earthquake, tsunami, etc. ambient air may contain chemicals and particles that may cause nuisance to human health, namely particulate matter (PM), ozone (O₃), volatile organic compounds (VOCs), sulfur dioxide (SO₂), nitrogen dioxide (NO₂) and carbon monoxide (CO) (**Fig.1**). When generated at ground-level, Ozone is a health hazard. It is formed by the reaction of the sunlight with pollutants such as nitrogen oxides (NO_x) from vehicles during traffic and fromindustries. That will result in higher levels of ozone pollution, occurring mainly during periods of sunny weather (WHO 2018).

Furthermore, when considering the adverse effects of air pollutants on the respiratory health, high concentrations of fine particles such PM_{2.5}, VOCs, SO₂ and NO₂ cause an increase in oxidative stress and airway inflammation. Due to their toxic effects in humans, concentrations of those air pollutants should be monitored regularly and below the normal exposure limits.

3. Burden of Environmental Air Pollution: Epidemiologic Profile of common AAP-attributable Lung Diseases

3.1. Rhinitis, Asthma and chronic bronchitis

Outdoor and indoor air pollution are known to exacerbate pre-existing allergic and non-allergic respiratory disorders, including rhinitis, asthma and chronic bronchitis. On the other hand, studies have also suggested that AAP can contribute to or induce the onset of those diseases (Guarnieri and Balmes, 2014). In addition, evidences have been accumulated in regard to the exacerbation of asthma by outdoor air pollution, with several studies suggesting a contribution to new onset of asthma as well. A time series by Bae and Kwon (2019) in Seoul suggested that an increase in PM₁₀, SO₂, NO₂, CO, and O₃was associated with significant increase of the risk for children's asthma hospitalization.

Our recent study that explored the respiratory health of female stone quarry workers in southern Congolese province of Katanga showed markedly higher ambient PM2.5 levels (8.2 times higher than WHO's occupational health limit) in quarry sites scattered across the town of Lubumbashi, as compared to control sites (public offices and public markets). Prevalence of all respiratory symptoms was also higher in dust-exposed stone quarry workers than in controls, with significantly reduced lung function (**Fig.2**) (Congo Environment and Health Research Team, 2019).



Fig.2- Peak expiratory flow rates of female quarry workers and controls (A) and images of quarry sites in Lubumbashi, DR Congo (B, C) (source: (Congo Environment and Health Research Team, 2019). This study was selected by the American Thoracic Society (ATS conference 2019) for Margaret Berklake award 2019 in Dallas, USA.

3.2. Chronic Obstructive Pulmonary Disease (COPD) and lung cancer

COPD is a progressive lung disease characterized by a persistent inflammatory response that, in general, cannot be reversed and leads to progressive decline in lung function and death. Tobacco smoking is a well-known cause of COPD; however, several studies have suggested that AAP is an important factor in the development of this lung disease (Marino et al., 2015). Recent studies have shown that higher COPD mortality rates and DALYs in South-East Asia region with 39 deaths per 100,000 people and 791 DALYs per 100,000 people, followed by Western Pacific region with 25 deaths per 100,000 people and 421 DALYs per 100,000 (Babatola, 2018). Regarding cancer of the respiratory tract, it was observed that South-East Asia and the Eastern Mediterranean regions had an increase in AAP-attributable cancers of the trachea, bronchus and lung in the last two decades, whereas rates of those cancers remained stable in African region. Moreover, WHO estimates that 6% of lung cancer deaths were caused air pollution in 2016 (WHO 2018).

3.3. Silicosis (Pneumoconiosis)

Silicosis is one of lung diseases caused by environmental or occupational exposure to dust. It is an interstitial pulmonary disease secondary to the inhalation of crystalline silica (silicon dioxide: SiO₂), usually in the form of quartz. It is one of the world's oldest known occupational diseases characterized by irreversible, progressive and almost always fatal; no specific treatment exists, although a small minority of patients may undergo lung transplantation. This lung disease can occur after weeks, a few years, 10 years or more following environmental or occupational exposure to silica, depending on the amount and concentration of inhaled silica dust. Silica is the second most abundant element that forms the quarter part of the earth's crust; thus, it is a ubiquitous mineral in human environment (Ngatu et al., 2012; The Lancet Respiratory Medicine, 2019). The mining and construction sectors that involve drilling, cutting, grinding or crushing the earth's crust or rocks are obviously associated with high level of silica exposure in both occupational and non-occupational environments. Hazardous exposures to silica dust often occur also informal and industrial operations such as sandblasting, rock drilling, road and tunnel construction, pottery making and masonry (Bang et al., 2015).

In many developing countries, such as in Africa and Asia, mining business and minerals processing industries represent the main source of income for the governments. However, it is very common to find employers who do not care about the work safety conditions of the workers, and employees perform their daily tasks without using any appropriate personal protective equipment (PPE) (Ngatu et al., 2012). This fact put them at high risk of occupational lung diseases; in case the silica dust goes into the lung parenchyma or reaches the alveoli, Silicosis may develop with high risk for lung cancer.

Chest radiographs (CXR)

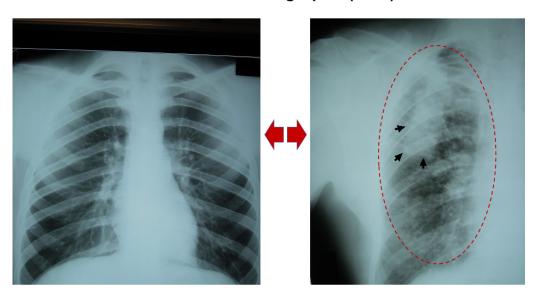


Fig. 3- normal (left), silicosis patient's CXR (right) with round opacities and progressive massive fibrosis (PMF) (with courtesy of Professor Kusaka Y.)

Recently, public concern regarding **ambient exposure to crystalline silica** has emerged. Non-occupational exposures to silica are rarely estimated or measured in community environment, given that it mainly occurs in residential areas located in the vicinity of silica-processing industries (Bhagia, 2012) such as cement producing plants and other construction settings. Silicosis has been established as carcinogenic by the International Agency for Research on cancer in 1997; this means that it can cause lung cancer. A number of cohort studies have confirmed the relationship between silica dust exposure and lung cancer risk, with a standardized mortality ratio (SMR) between 1.37 and 3.70; some of those reports showed stronger associations with excess mortality from lung cancer among silicotics (Scarselli et al., 2011; Erren et al., 2009; Pelucchi et al., 2006). Hence, doctors or clinicians should keep in mind the relationship between a workplace with exposure to silica dust and the development of other respiratory diseases such as lung cancer (Ngatu et al., 2012).

The most common radiological feature that can be seen on chest radiographs (CXR) or computed tomography (CT) films is presence of 'silicotic nodules' (Ngatu et al., 2012; Bhattacharya et al., 2016). However, the nodules may coalesce and form a 'large opacity' known as 'progressive massive fibrosis' or PMF (**Fig.3**).

4. Solutions to Ambient Air Pollution-associated Respiratory Diseases?

4.1. Prevention

There is a saying that 'prevention is better than cure'. Preventive measures should target both outdoor and indoor air pollution. They comprise, but not limited to:

(1) For industries:

➤ Use of clean technologies susceptible to reduce industrial air pollutants emissions; elimination of hazardous gas accumulated in the atmosphere.

(2) Transport (traffic):

➤ A shift to clean power engines; promotion of walking and cycling (exercise) in communities whencommuting to school or workplace.

(3) Agriculture:

➤ Policies for wastes reduction, their recycling and possibly re-use; avoidance of use of pesticides or chemical fertilizers.

(4) Power generation:

➤ Use of fuels with low emissions fine particulate matter and other air pollutants; use of environment-friendly sources of energy. Reducing greenhouse gas emissions would have a major co-benefit in lowering primary and secondary emissions of air pollutants.

(5) Daily life in residential and working environment with air pollution:

- Monitoring atmospheric concentrations of air pollutants (Air Quality Monitors are available in the market).
- > Periodic risk assessment and improve work safety in occupational settings
- ➤ Use of appropriate personal protective equipment/devices such as masks (not all masks are appropriate as they may let fine particles, even viruses and bacteria pass through; N95 masks are strongly recommended).
- ➤ Regulation and law enforcement for economic, entertaining,... activities that generate air pollutants.

(6) Health education sector and Health system:



Fig.4- Periodic lung function (Spirometry) testing for elderly in remote areas (source: the author)

- ➤ Provide basic knowledge on Environmental health risks and diseases to future health care providers.
- Train specialists in Environmental and Occupational health, particularly in low- and middle-income countries; dispatching specialists train others for capacity building so as to identify and control environmental hazards and manage their adverse effects on humans in communities.
- ➤ Periodic medical check-up for respiratory health explorations in communities and occupational settings at high risk of AAP-associated lung diseases (spirometry, lung auscultation, eventually radiological investigation) (**Fig.4**).

4.2. Management of AAP-associated Respiratory Diseases

Most of respiratory inflammatory diseases can be managed in clinics and hospitals. However, COPD and Silicosis are chronic conditions that are currently considered incurable. Regarding Silicosis, recent clinical trials have shown improvement of patients' health in terms of reduction of airway inflammation and symptoms (Sun et al., 2019). But, reversing the disease course seems still not at hand dream. Nonetheless, avoidance of exposure to triggers (tobacco smoke and other air pollutants) may slower disease progression and, possibly, the occurrence of complications.

5. Acknowledgments

We thank Professor Simon Bedelo Mpungi and 'DR Congo Environment and Health Research Team' members for their support and advices during the preparation of this paper.

6. Conflict of interest declaration

No conflict of interest related to this paper.

7. References

- 1. Pruss-Ustun A, Wolf J, Corvalan C, Bos R, Neira M. "Preventing disease through healthy environments. A global assessment of the burden of disease from environmental risks." World Health Organization, Geneva 2016.
- 2. Landrigan PJ. "Air pollution and health." Lancet 2017; 2(1): E4-E5.
- 3. Perera F. "Pollution from fossil-fuel combustion is the leading environmental threat to global pediatric health and equity: solutions exist." *Int J Environ Res Public Health* 2018; 15(1): 16.
- 4. "Global Burden of Disease (GBD) Risk Factors collaborators 2015. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015." *Lancet 2016*; 388 (10053): 1659-1724.
- 5. World Health Organization (WHO). "Noncommunicable diseases and air pollution" (WHO Report 2019). Available at: http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2019/noncommunicable-diseases-and-air-pollution-2019
- 6. World Health Organization (WHO). "Ambient air pollution" (WHO Report 2018). Available at:https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health
- 7. The World Bank. "Cost of pollution in China." Washington, DC: World Bank report 2007. Available at: Available at:https://www.worldbank.org/en/news/press-release/2007/07/11/statement-world-bank-china-country-director-cost-pollution-china-report
- 8. Marino E, Caruso M, Campagna D, polosa R. "Impact of air quality on lung health: myth or reality?" *Ther Adv Chron Dis 2015*; 8(6): 286-296.
- 9. Chen SJ, Hsieh LT, Kao MJ et al. "Characteristics of particles sampled in southern Taiwan during the Asian dust storm periods in 2000 and 2001." *Atmos Environ 2004*; 38: 5925-5934.
- 10. Bell ML, Levy JK, Lin Z. "The effect of sandstorms and air pollution on cause-specific hospital admissons in Taipei, Taiwan." *Occup Environ Med 2008*; 65:: 104-111.
- 11. Yu HL, Chien LC, Yang CH. "Asian dust storm elevates children's respiratory health risks: a spatiotemporal analysis of children's clinic visits across Taipei (Taiwan)." *Plos One 2012;* 7(7): e41317.
- 12. Shima M. "Health effects of air pollution: a historical review and present status." *Nihon Eiseigaku Zasshi 2017*; 72(3): 159-165.
- 13. Nakao M, Yamauchi K, Mitsuma S et al. Prev Med Public Health 2019;52:416-426
- 14. Bae S, Kown HJ. "Current state of research on the risk of morbidity and mortality associated with air pollution in Korea." *Yonsei Med J 2019*; 60(3): 243-256.
- 15. Katoto PDMC, Byamungu L, Brand AS, et al. "Ambient air pollution and health in Sub-Saharan Africa: current evidence, perspectives and call to action." *Environmental Research 2019*; 173: 174-188.

- 16. Ngatu NR, Kayembe JMN, Suganuma N. "The Pneumoconiosis." In: *Lung diseases; Intech*, 2012.
- 17. Leon-Kabamba N, Ngatu NR, Christophe-Nyembo M et al. "Silicosis in underground miners in Lubumbashi, Democratic Republic of the Congo: 27 cases » (published in French). *Medecine et Sante Tropicales 2018*; 8(4): 395-8.
- 18. Ngombe Kabamba L and DRC Team. "Women struggling for survival amidst severe crisis: deleterious effects of chronic dust-exposure on respiratory health of female stone quarry workers in Lubumbashi." Available at:https://www.atsjournals.org/doi/abs/10.1164/ajrccmconference.2019.199.1_MeetingAbstracts. A4259
 - 19. Leon-Kabamba N, Ngatu NR, Kakoma SJ et al. « Respiratoryhealth of Congolese coltan miners. »Available at: https://www.ncbi.nlm.nih.gov/pubmed/29951778/
 - 20. Congo Environment and Health Research Team. "Women struggling for survival amidst severe crisis: deleterious effects of chronic dust-exposure on respiratory health of female stone quarry workers in Lubumbashi." Available at:https://www.atsjournals.org/doi/abs/10.1164/ajrccmconference.2019.199.1_MeetingAb stracts.A4259
- 21. Bio FY, Jackson C, Burge PS. "Respiratory symptoms and lung function impairment in underground gold miners in Ghana." *Ghana Med J* 2007; 41(2): 38-47.
- 22. Bateman C. "Silicosis-10,000 gold miners getting set to sue." S Afr Med J 2012; 102(6):338–340.
- 23. Kabamba LN, Ngatu NR, Kayembe JMN et al. "Silicotuberculosis in African underground miners." *Ann Afr Med 2016*; 9(2): 2218-2226.
- 24. Guarnieri M, Balmes JR. "Outdoor air pollution and asthma." *Lancet 2014*; 383(9928): 1581-1592.
- 25. Babatola SS. "Global burden of diseases attributable to air pollution." *J Public Health Afr* 2018; 9(3): 813.
- 26. The Lancet Respiratory Medicine (Editorial). "The world is failing on Silicosis." Available at: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30078-5/fulltext
- 27. Bang KM, Mazurek JM, Wood JM et al. "Silicosis mortality trends and new exposures to respirable crystalline silica United States, 2001-2010." *MMWR Morb Mortal Wkly Rep.* 2015 Feb 13; 64(5): 117-20.
- 28. Bhagia LJ. "Non-occupational exposure to silica dust." *Indian J Occup Environ Med 2012*; 16(3): 95-100.

- 29. Scarselli A, Binazzi A, Forastiere F, Cavariani F, Marinaccio A. "Industry and job-specific mortality after occupational exposure to silica dust." *Occup Med* (Lond) 2011; 61(6): 422-9.
- 30. Erren TC, Glende CB, Morfeld P et al. (2009). "Is exposure to silica associated with lung cancer in the absence of silicosis? A meta-analytical approach to an important public health question." *Int Arch Occup Environ Health* 2009; 82(8): 997-1004.
- 31. Pelucchi C, Pira E, Piolatto G et al. "Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996-2005." *Ann Oncol 2006*; 17(7): 1039-1050.
- 32. Batthacharya S, Dey A, Pal A et al. "Silicosis in the form of progressive massive fibrosis: a diagnostic challenge." *Indian J occup Environ Med 2016*; 20(2): 114-117.
- 33. Sun J, Song P, Wang Y, Chen Y. "Clinical efficacy of acetylcysteine combined with tetrandrine tablets in the treatment of silicosis and the effect on serum IL-6 and TNF-α." *Exp ther Med 2019*; 18(5): 3383-3388.