

Silica exposure and its effect on the physiology of workers



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Introduction

Pneumoconiosis is derived from the Greek word ***Pneumon*** meaning "lung" and ***konis*** meaning "dust". It therefore specifically refers to lung disorders that result from the inhalation of dust. It is, however, important to note that only dust that contain crystalline quartz have the potential to induce silicosis. The outcome of exposure to dust that contains silica quartz is fibrosis of the lungs. The disease that develops due to free silica exposure is fibrotic pneumoconiosis and the lung disease that develops because of crystalline silica exposure is known as silicosis. Silicosis is a non-curable irreversible disease. Crystalline silica is currently classified as a Class 1 substance by the International Agency for Research on Cancer (Ref.1). This classification indicates that a causal relationship must exist between exposure and the development of human cancer. It can, however, be prevented if proper dust control measures are employed. If dust levels cannot be contained within acceptable levels, the correct utilisation of approved personal protective equipment can be effective in silicosis prevention.

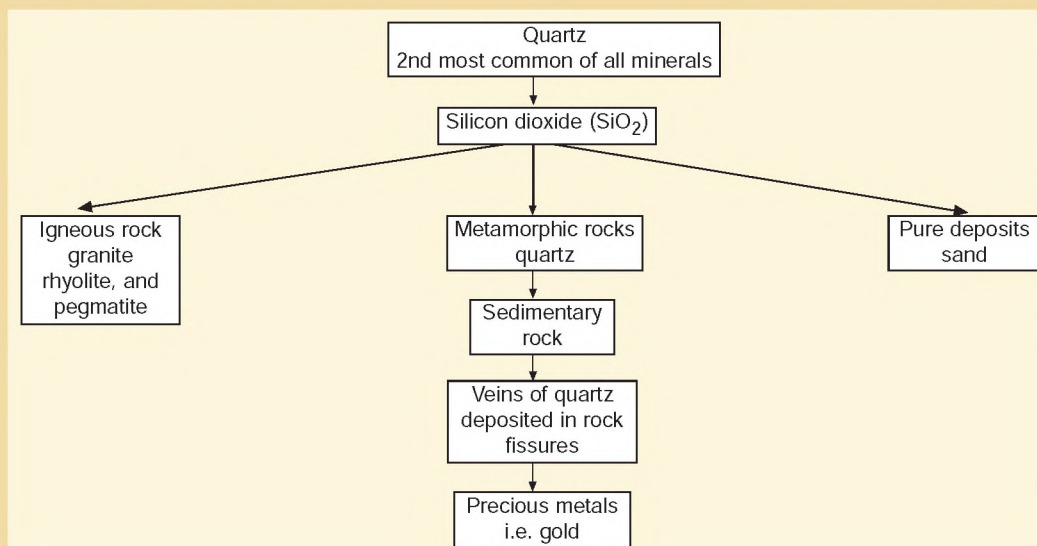
Who are at risk to develop silicosis?

Workers most prone to develop silicosis are workers who are exposed to natural occurring minerals in crystalline form. Hnizdo and Sluis-Cremer (Ref.2) concluded that the risk to develop silicosis increase exponentially with an increase in cumulative dose of silica dust. There are seven recognised crystalline silicas with trace amounts of metals i.e., quartz, cristobalite, tridymite, coesite, stishovite, moganite and melanphlogite. The most commonly found in industry and naturally occurring crystalline forms of silica are quartz, cristobalite and tridymite. It is however important to note that non-industrialised mixed dust exposure, as commonly found during agricultural activities, can also lead to a significant silica load in the lungs of farm animals and humans (Ref.3). Mechanised and manual harvesting activities of some crops can result into exposures as high as 0.1 – 0.65 mg/m³ (Ref.4);(Ref.5).

Distribution and characteristics of crystalline silica

Quartz is the second most commonly found mineral and consists of SiO₂ and it can be found in almost every type of rock on earth. Rocks with more than 47 % SiO₂, contain quartz (Ref.6). The type of rocks with large quartz content include igneous rock (granite, rhyolite, pegmatite), metamorphic rock (quartz) and in pure deposits (sand) (**Figure 1**). Quartz form veins in sedimentary rock.

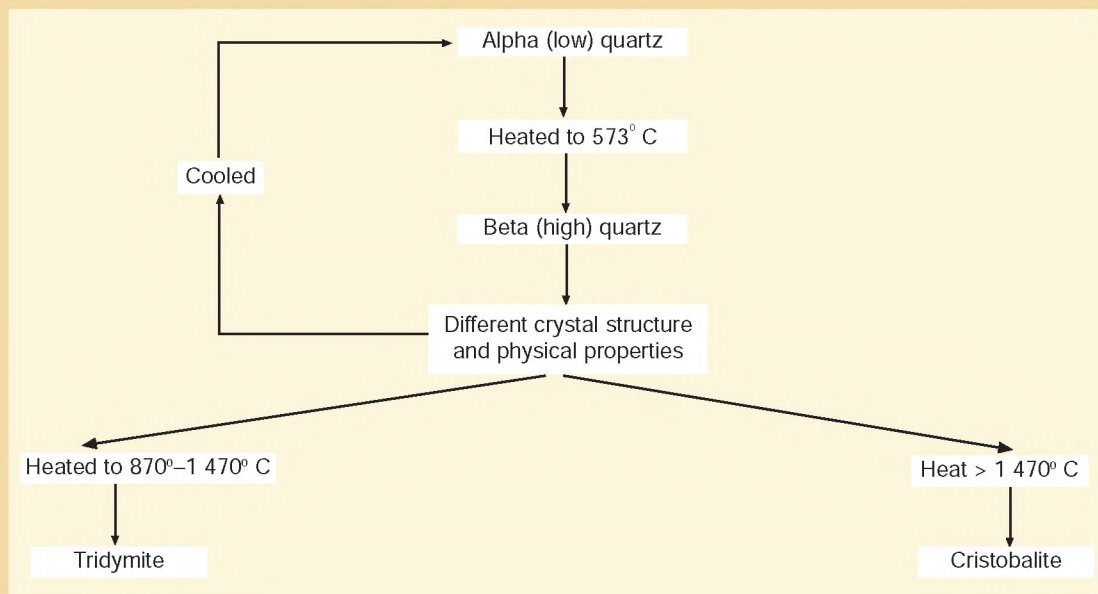
Figure 1: Distribution of quartz in the various types of rock and other deposits



These veins deposited in rock fissures form the matrix for precious metals i.e., gold. Gold is therefore mainly found in quartz veins. It can therefore be expected that mining of gold will lead towards significant release of quartz. In South African mines the rock generally contains 60 – 90% SiO₂ in the crystalline form of quartz (Ref.2).

Alpha (low) quartz is the type of silica that is most often released during mining, blasting and construction activities. Cristobalite is associated with ceramic, refractory and diatomaceous earth industries. Cristobalite can also be formed due to processing of crude materials that involve heating to high temperatures. It is therefore important to note that silica quartz can be transformed during industrial processes, especially if heated, and this can change the crystalline structure (Figure 2).

Figure 2: Influence of heating and cooling on the crystalline structure of quartz



The transformed crystalline structure is more pathogenic or toxic than the original alpha quartz crystalline structure. If the heating process does not exceed 578°C, beta (high) quartz are formed. It will, however, revert to its original structural and physical property if cooled. If the heating process exceeds 578°C but are lower than 1 470°C, tridymite will form. Temperatures beyond 1 470°C will result in the formation of cristobalite. Neither of the last two transformed structures can revert to alpha quartz. The melting point of transformed quartz is about 1 710°C. This is the primary reason why sand is used as moulds because its melting point is higher than most of the metals that are usually used for casting processes (Ref.7).

Factors that influence toxicity and potential to induce fibrosis by crystalline silica

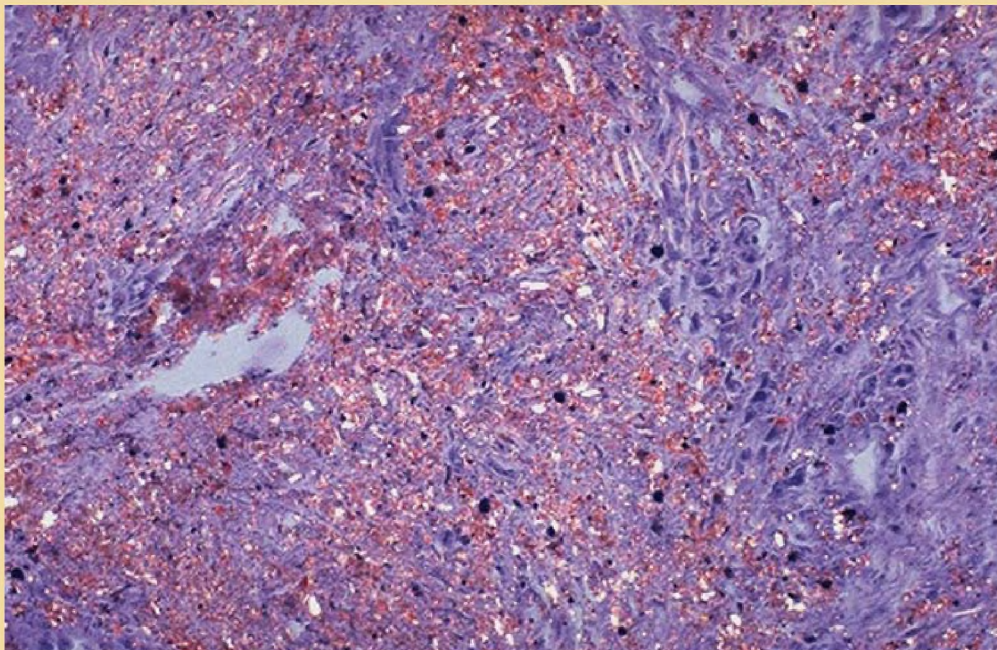
Quartz, cristobalite and tridymite have the highest potential to introduce fibrosis in the lungs. The biological reactivity of the three types of crystalline silica is not similar. Quartz potential to induce fibrosis is higher than tridymite and tridymite's potential to induce fibrosis is higher than cristobalite (Ref.8). Freshly fractured quartz proved also to have an increased potential to induce a fibrotic reaction in lung tissue compared to that of "aged" quartz. The presence of radicals on the fracture surface is the primary determinant in terms of toxicity. SiOH groups on the surface of crystalline silica are capable to form hydrogen bonds with membrane components. The hydrogen bond formation leads to membrane damage and therefore disruption of cellular integrity (Ref.9). Due to

the decay of radicals on the fracture surface of quartz, the potential of the quartz particle to cause fibrosis, is reduced (Ref.10). Presence of aluminum and iron on the mineral lattice of the crystalline structure of "aged" quartz renders the particle also to be less fibrotic (Ref.11,12). The yield of OH radicals decrease by more than half if the silica particles are stored in air for four days (Ref.13). Particle size also play an important role in terms of toxicity. Large particles with a size of $> 0.5\mu\text{m} - 2\mu\text{m}$ is of importance in the development of silicosis (Ref.14). Earlier reports did however indicate those particles with sizes less than $1\mu\text{m}$ are the most pathogenic (Ref.15). The geographical area may also play a role in the fibrogenic properties of the crystalline silica. Hnizdo and Sluis-Cremer (Ref.2) commented that quartz in the South African mines may be more toxic than Canadian quartz. They stated that this may have serious implications as international threshold limit values (TLV's) or occupational exposure limits (OELs) might be too high and therefore not safe to be used in the South African gold mines.

Pathology associated with crystalline silica exposure

Silica quartz crystals in lung tissue can be observed under polarised light microscopy. **Figure 3** illustrates a slide under polarised light microscopy of lung tissue containing crystalline silica quartz. The white spots represent silica crystals in the specimen of lung tissue. The silica crystals present in the lung tissue are of different size and represent therefore a typical picture of silica crystal distribution in lung tissue of a worker exposed to crystalline silica.

Figure 3: Lung tissue observed under polarised light microscopy containing crystalline silica (Ref.26)



As already mentioned, the outcome of crystalline silica exposure leads to silicosis. Silicosis is a slowly progressive disorder and usually takes more than 10 years to develop and may progress after a worker's exposure to silica has ended. The majority of miners develop radiological signs of silicosis only when they are over 50 years. (Ref.2). An exposed worker will either develop acute, accelerated or chronic silicosis. The main determinant of the type of silicosis is however the worker's level of exposure. Workers exposed to high concentrations of fine particulate matter as crystalline silica will be more prone to develop acute or accelerated silicosis. Chronic silicosis is mainly the result of long-term exposure to silica. With acute, accelerated and chronic silicosis,

death occurs after a few months, 5-10 years and more than 10 years respectively. **Table 1** summarises different occupations that are known to be associated with acute, accelerated and chronic silicosis.

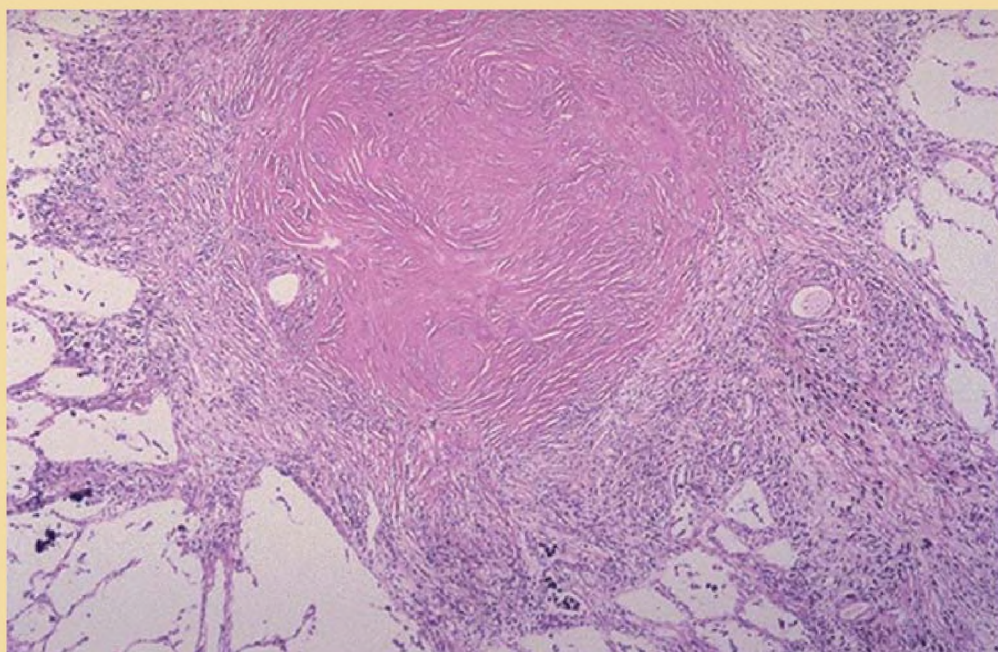
Table 1: Difference types of silicosis associated with different occupations (Ref.8)

Type of silicosis	Occupation
Acute	Sandblasting, surface drilling, tunneling, silica flour milling, ceramic making, grinding
Accelerated	Silica flour mill operations, sandblasting and other mechanically and crushing operations
Chronic	Inhalation of crystalline silica over prolonged periods, + 10 years of exposure to dust containing 18-30% crystalline silica

Workers with silicosis are furthermore prone to develop other lung diseases due to the fibrotic effect crystalline silica have on lung tissue. Other lung diseases associated with crystalline silica exposure are increased mycobacterium infections i.e., tuberculosis, bronchogenic carcinoma and immune-mediated diseases i.e., scleroderma. A lifetime exposure to the current Occupational Safety and Health Association (OSHA) standard of 0.1 mg.m³ increase the likelihood to develop lung cancer by 30%. Recently there are indications that nephrotoxicity in workers who are exposed to silica are linked with quartz exposure. There exist numerous case reports linking acute glomerulonephritis with accelerated silicosis (Ref.11). Hotz et al. (Ref.16) mentioned that sub-clinical effects on kidney function may occur in workers who are exposed to silica for short periods. Of the mentioned diseases only silicosis, tuberculosis and bronchogenic carcinoma are compensatable diseases.

A primary feature that develops in lungs of silica quartz exposed workers is nodule formation in the upper zones of the lung (Ref.17). Nodule formation is usually the result of many years of exposure to relatively low levels of dust that contain silica quartz (Ref.18).

Figure 4: A microscopic photo of a typical silicotic nodule containing collagen fibres in a whorled pattern (Ref.27)



The nodules are connective tissue arranged in a whorled pattern, similar to that seen if an onion

is being cut in half. The macrophages that contain the silica quartz crystals are present at the periphery of the nodule with an accumulation of collagen fibres in the center. With time, the collagen fibres arranged themselves into concentric configurations and can become hyalinised over time. The center of the nodule can as a result of this, become deprived of blood supply and therefore also oxygen delivery and can result into necrosis of the tissue in the center of the nodule (Ref.11).

Figure 4 represents a photo of a silicotic nodule. The number of nodules increases with the degree and length of exposure respectively to silica. A typical silicotic nodule have the following characteristics: Central zone = whorls of dense, hyalinised. What does it mean? (glassy or transparent) fibrous tissue, midzone = concentrically arranged collagen fibres similar to onion skinning feature, periphery or outer zone = randomly orientated collagen fibres, mixed with dust loaded macrophages and lymphoid cells. Under polarised light microscopy, crystalline material can be observed in the center of the lesion (Ref.11). The degree of restrictive lung disease is also related to the degree and length of crystalline silica exposure. The number of nodules increases with the degree and length of exposure.

Other pathological features of silicosis are that the pleura of the lungs can be adherent and thickened. This is therefore the primary reason why workers diagnosed with silicosis will present a lung function test outcome that indicate towards a pulmonary lung restrictive disease. Under autopsy, the lungs may have a gritty feeling.

Theories related to the pathogenesis of silicosis

There are currently three theories relating to the pathogenesis of silicosis namely:

- Piezoelectric theory
- Solubility theory
- Theory regarding damage to the alveolar macrophage.

Attention will only be given to the last theory i.e. damage to the alveolar macrophage as this is currently the mostly accepted theory.

The influence of silica on the lung can be summarised in the following flow diagram (**Figure 5**).

Figure 5: Influence of silica exposure on alveolar macrophage in the lung

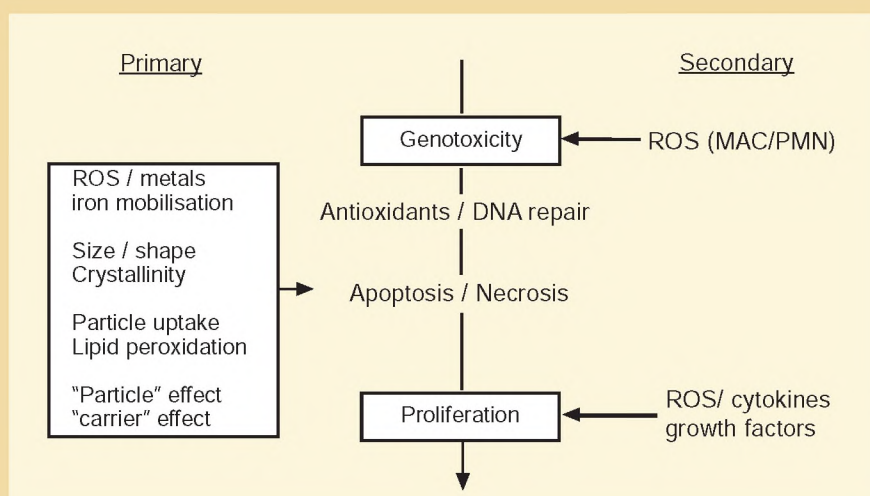


If free silica reaches the alveolar macrophage it is engulfed or phagocytosed by the alveolar macrophage which may lead to damage of the lysosomal membrane. This is mainly due to the

interaction between crystalline silica and hydrogen ions in membranes of cells. The peroxidation of the phospholipids and unsaturated fatty acids in the membranes of the cellular and intracellular structures, results in damage of the membranes and the generation of oxygen-free radicals (Ref.11) which cause damage to intracellular structures. A result of this is that the membrane structures of the cells become more leaky (permeable) and ions move more freely over the cellular membranes. This renders the cells more vulnerable to chemical and physical stressors. Due to the damage to the intracellular structures, proteolytic enzymes are released into the cytoplasm that results in the death of the macrophage. The destruction of the alveolar macrophages leads to increased proteolytic enzyme release in the lung tissue. The outcome of this is the initiation of fibrotic reactions in the lung.

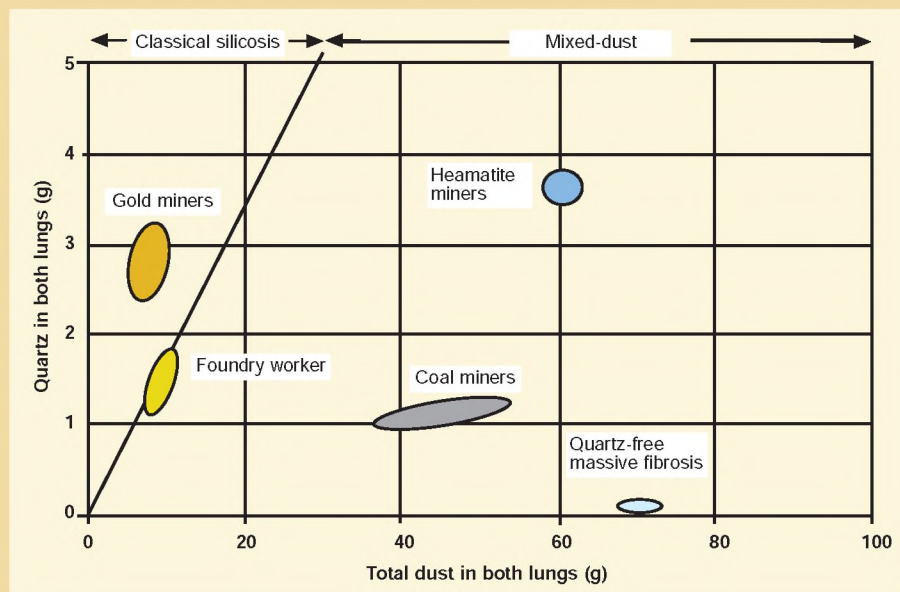
Continued silica exposure and therefore frequent damage to alveolar macrophages leads to an alteration in macrophage function. This leads to activation of humoral and cellular immunity mechanisms and the release of certain inflammatory cytokines e.g., IL-1, free radicals and growth factors (Ref.19); (Ref.20). This stimulates collagen synthesis and production of antibodies against collagen. The anti-collagen antibody stimulates the fibroblasts to produce more collagen formation that eventually leads to nodule formation. Due to the alteration in macrophage function, it is now accepted that quartz exert a genotoxic effect on human cells. Quartz exposure can have a direct, primary genotoxic effect, or an indirect or secondary genotoxic effect because of the inflammation process. **Figure 6** summarise all the factors, as already been discussed in the preceding text, that constitute the primary and secondary genotoxic effects quartz may have in the lungs of exposed workers.

Figure 6: Primary and secondary genotoxic effects of crystalline silica on lung tissue (Ref.28)



Antioxidants and DNA repair mechanisms can restore or reduce the genotoxic effect of particles due to the release of Reactive Oxygen Species (ROS) because of primary and secondary genotoxic mechanisms. If the antioxidant and DNA repair mechanisms are ineffective, the genotoxic effect may lead to apoptosis and necrosis. The increase in apoptosis is dose-dependent and it is described by Lim et al. (Ref.21) to play a role in the silica induced inflammatory process and chronic fibrosis. Apoptotic cells, cells that are programmed to die, and necrotic cells, cannot be repaired. **Figure 7** illustrates the relationship between total dust load and classical silicosis. A low total dust exposure results in a much higher incidence of classical silicosis in gold miners and foundry workers compared to coal and haematite, a principal ore of iron, consisting mainly of iron (III) oxide, Fe₂O₃. A possible explanation for this is that the absorption of other dusts or their constituents onto the silica surface lead to a decrease in silica toxicity and therefore the pathologic response (Ref.11). This confirms the already discussed phenomenon that the surfaces of the crystalline structure play a significant role in the pathogenic potential of the structure.

Figure 7: Relationship between total dust load and quartz content in lungs of workers employed in different "dusty" industries. Redrawn from: (Ref.29)



Diagnosis of silicosis

The gold standard to diagnose silicosis is by means of a chest X-ray. Lung function tests, sputum analysis and lung biopsies can also be used.

The application of lung function tests is however not reliable as most patients do not show changes in lung function tests if silicosis is diagnosed. Symptomatic patients do however show signs of dyspnea. It is however important to note that this occurs only with extensive fibrosis of the lungs. Recently the application of biomarkers as indicators of silica exposure received more attention. Biomarkers, that are biological measurable indicators or products of physiological processes that represent a critical step in the development of toxicity, show promise as a diagnostic tool for silicosis. Specific biomarkers can be sampled from blood, urine, sputum or saliva. The concentration of a specific peripheral biomarker needs however to be selective for a specific organ and associated occupational disease. The advantage of the utilisation of sensitive biomarkers is that early changes can be detected on cellular or molecular level. If a biomarker has a high sensitivity, changes in the concentration of a biomarker will precede changes in functional physiology and morphology of a specific organ.

The development of pathophysiological processes that can result in morphological organ changes can therefore be prevented. Due to the sensitivity of biomarkers, regular sampling of body fluids from workers by occupational health personnel may detect early lung pathology that may be indicative of lung damage. Epidemiological application of a battery of immunoassays that include ligandin, carbonic anhydrase, alanine aminopeptidase, adenosine deaminase-binding protein and intestinal alkaline phosphatase, fibronectin and Tamm-Horsfall glycoprotein proved to be sensitive to indicate early effects on the different segments of the nephron after crystalline silica exposure (Ref.22). A microprotein also found in the urine i.e., Clara cell protein (CC16) showed promise as a biomarker for lung toxicity (Ref.22). Bernard et al. (Ref.23) did indicate that a decline in serum Clara Cell protein (CC16) levels can be used to detect early toxic effects of silica exposure in workers exposed to silica. CC16 is a low molecular weight protein that is released by the Clara cells in the lungs and it has been suggested that CC16 might play an important role in the lung as a natural immunosuppressor and anti-inflammatory agent (Ref.24); (Ref.25). Bernard and Hermans (Ref.22) stated that the use of biomarkers is becoming one of the key elements in disease

prevention that are associated with occupational and environmental pollutants. Castranova and Vallyathan (Ref.8) also emphasised that innovative research strategies will be vital to identify susceptible individuals who have an increased risk to develop e.g., pneumoconiosis and specifically silicosis. Hnizdu and Sluis-Cremer (Ref.2) also alluded to the fact that there are a group of workers who are more susceptible to develop silicosis at a younger age.

Conclusion

To conclude it is important to take note that silicosis is a non-curable occupational disease. Silicosis is however a preventable disease and can be prevented if proper primary and secondary prevention strategies are in place. Primary prevention strategies include proper ventilation, dust collectors, wetting techniques and the use of substitutes for quartz containing materials in operations such as sand blasting. Secondary prevention strategies include the use of approved personal protective equipment (PPE), training of the workers and medical examinations. The only effective strategy therefore to prevent silicosis is to take actions to avoid inhalation of crystalline silica dust. The importance to train management and workers, as a mechanism to prevent silicosis can however not be over emphasised. Only if management and workers realise the debilitating effects of silica quartz exposure, and take ownership of the National Programme for the Elimination of Silicosis (NPES) from the workplace, will it be possible to reach the goal of no occupational related silicosis cases by 2030.

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