

Review of Pulmonary Effects of Poly(vinyl Chloride) and Vinyl Chloride Exposure

by Ruth Lilis*

The contributions of several recent reports to the definition of pulmonary effects of PVC dust inhalation are reviewed. Granulomatous reaction, with inclusion of PVC particles in macrophages and histocytes, and associated interstitial pulmonary fibrosis have been found to lead to exertional dyspnoea, diffuse micronodular chest radiographic opacities and restrictive pulmonary dysfunction.

The effects of vinyl chloride (VC) monomer (gas) on proteins and the immunologic mechanisms triggered by the altered protein are possible mechanisms for the development in some cases of interstitial pulmonary fibrosis secondary to VC exposure.

Vinyl chloride, a confirmed carcinogen, has been associated with, among other malignant tumors, a significant increase in the incidence of lung cancer. The magnitude of this effect has not yet been completely evaluated.

Several recent reports (1-3) have contributed new observations on pulmonary disease in vinyl chloride (VC)- and poly(vinyl chloride) (PVC)-exposed patients.

Earlier reports, a few even preceding the identification in 1974 of vinyl chloride as a human carcinogen (with hemangiosarcoma of the liver the marker tumor, but most probably not the only tumor), had centered on the rather unexpected occurrence of pulmonary radiologic abnormalities (4-8) or pulmonary function impairment (4, 9-12) or had indicated dyspnea as a prominent symptom (11, 13) in VC and/or PVC exposed workers.

The radiologic pattern first described in 1975 (5) was essentially that of reticular-linear and/or nodular (small rounded) opacities, involving both lungs, predominantly in the lower zones.

Pulmonary function abnormalities reported have been both restrictive and obstructive dysfunction with diffusion defects and arterial desaturation in some cases.

Three recent reports, one a case report (1), the other two epidemiologic surveys (2, 3), seem to identify PVC dust as the etiologic agent in a

peculiar type of pulmonary fibrosis associated with a granulomatous reaction.

Exertional dyspnea, diffuse micronodular chest radiographic abnormalities and restrictive pulmonary dysfunction, were the main characteristics in the case of PVC pulmonary fibrosis associated with granulomatous lesions (1).

Electron microscopic examination of lung tissue showed giant multinucleated cells containing a nonhomogeneous material in their cytoplasm, which was identified to be PVC (1). A similar pattern was reproduced by incubation of human macrophages obtained by bronchial lavage, with PVC powder: absorption of PVC particles in the cytoplasm was rapid, with thinly granular lysosomal material deposited against the PVC particles.

Similar histologic lesions had been previously described in a human case (4) and in an experimental study in guinea pigs and rats (14). In another experimental study, intratracheal administration of PVC dust in rats (15) has been shown to result in an increase in the activity of lysosomal enzymes, interstitial fibrosis and granulomatous lesions surrounded by fibroblasts, reticulin and collagen fibers.

An epidemiologic study of a large group of workers exposed to PVC and VC (2) detected 20 cases of "typical pneumoconiosis," i.e., chest x-ray changes consisting in irregular opacities or micronodular shadows of at least class 1 profusion,

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according to the ILO U/C Classification. All these cases were found among PVC exposed employees. The pattern of radiologic abnormalities described is very similar to that reported in the case in which the lung biopsy revealed fibrosis and granulomatous reaction, with inclusion of PVC particles.

The same study reported the presence of less marked radiologic abnormalities, of the linear-reticular type, in a much larger proportion (32%) of the population examined; these changes were present both in VC monomer exposed and in PVC exposed employees. While the prevalence was higher in smokers than nonsmokers, 65 of the 388 x-rays with linear-reticular opacities were found in persons who had never smoked.

In another large epidemiologic study (3), exposure to respirable PVC dust was found to be associated in a proportion of exposed workers with the presence of small rounded opacities on the chest radiograph and a decline in mean ventilatory capacity.

The question of pulmonary effects due to vinyl chloride monomer continues to be of great interest. The multi-organ effects of vinyl chloride include the peculiar syndrome of acroosteolysis, scleroderma-like skin changes, vascular changes affecting the arteries, arterioles and capillaries of hands and fingers, liver and spleen capsular fibrosis, liver fibrosis, abnormalities of the sinusoidal vessels in the liver, and portal hypertension. Ward (16) investigated the immunologic status of 58 workers from a VC polymerization plant. The findings included hyperimmunoglobulinemia, cryoglobulinemia, cryofibrinogenemia, *in vivo* complement activation via the classic pathway, with C₄ and C₃ conversion and an increase in the B cell lymphocyte population. Immunofluorescent examination of skin, muscle and lung biopsy specimens revealed the presence of circulating immune complexes, with deposition on the vascular endothelium and occlusion of small vessels. Immunoglobulin, complement and fibrinogen deposition in the subintimal regions of the vessel were found in areas with subintimal fibrosis and luminal occlusion.

Grainger et al. (17) have accumulated evidence suggesting the following mechanism: the vinyl chloride metabolite cyclic chloroethylene epoxide, an alkylating agent with high biological activity binds to IgG producing structural conformational changes that promote aggregation of IgG molecules. The modified IgG may also become antigenic. The IgG aggregates are cryoprecipitable and may initiate complement activation. Precipitation of IgG aggregates by cold leads to complement activation,

platelet aggregation and conversion of fibrinogen to fibrin with polymerization. Occlusion of small vessels results, and ischemia stimulates new collagen biosynthesis.

Similar abnormalities of the immunologic status were found in another study of 22 workers exposed to vinyl chloride, with Raynaud's syndrome and, in some cases, acroosteolysis. Latent cryoglobulinemia was detected in 18 cases, with increases of immunoglobulins, IgA and IgG (18).

Circulating cryoimmunoglobulins are a prominent feature of idiopathic pulmonary fibrosis (19) and increased IgG levels have been shown to be characteristic for bronchoalveolar lavage fluid of such patients.

Interstitial pulmonary fibrosis is a possible effect of vinyl chloride exposure. The occurrence of more dramatic and specific abnormalities in other organ systems—liver, spleen and peripheral circulation—has probably prevented more focused attention on pulmonary effects of vinyl chloride in the past.

Long-term effects of vinyl chloride include well documented carcinogenicity. Lung cancer has been found to occur with an increased incidence in several mortality studies (20-22). Abnormalities in sputum cytology tests have been found to be more frequent in VC/PVC-exposed workers than in other chemical industry employees and in smokers (23). In experiments on mice, Suzuki (24) has described hyperplastic changes of the alveolar lining cells and pulmonary tumors in the majority of exposed animals. The ultrastructure was thought to indicate that the tumors originated in type II alveolar cells. Alveologenic tumors were also described in several other experimental studies (25-27). Interestingly, other known carcinogens, such as polycyclic aromatic hydrocarbons, nitrogen mustard and chromates, produce pulmonary tumors in experimental animals similarly, originating in the type II alveolar cell.

The effects of vinyl chloride-poly(vinyl chloride) exposure on the respiratory system of exposed workers seem to indicate two patterns of nonmalignant effects: a granulomatous reaction to PVC dust, with inclusion of PVC particles in macrophages and histocytes and associated interstitial fibrosis, and an interstitial pulmonary fibrosis due to vinyl chloride monomer effects on protein molecules and the immunologic mechanisms triggered by the altered protein.

The long-term carcinogenic effect, with a significant increase in the incidence of lung cancer, also is of concern, although the magnitude of this effect has not yet been completely evaluated.

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