VINYLS' MEDICAL COMMITTEE

# The Influence of Polyvinylchloride on the Lungs (update 1999)


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# LIST OF ABBREVIATIONS

A.C.G.I.H.: American Conference of Governmental Industrial Hygienists

DOP: dioctylphthalate

$FEV_1$: Forced Expiratory Volume in one second

FVC: Forced Vital Capacity

hr: hour

I.L.O.: International Labour Organisation

I.O.M.: Institute of Occupational Medicine

M.R.C.. British Medical Research Council

O.S.H.A.: Occupational Safety and Health Administration

PEFR Peak Expiratory Flow Rate

PVC: polyvinyl chloride

$TL_{CO}$: gas transfer for carbon monoxide

VCM: vinyl chloride monomer

$V_{max75}$: maximum flow at 75% of expired vital capacity

wk: week

yr:year

# Contents

# Introduction

Within APME the Vinyls Committee asked the Vinyls Medical Committee to evaluate the influence of PVC dust on the lungs. In order to answer this question a Task Force was set up by the Vinyls Medical Committee. The remit of the Task Force is to review the literature about the potential biological effect of PVC dust on the lungs (excluding cancer) and to draft a report.

The Task Force could rely on the knowledge of Dr. G.M. Paddle (ICI) and Dr. G. Piggott (ICI) for the epidemiological and the toxicological issues respectively.

An update of the first report of 1993 with the relevant literature published untill the end of 1998 has been the purpose of this paper.

The members of the Vinyls Medical Committee are:

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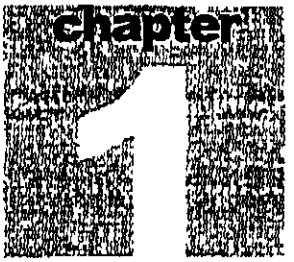



# ANIMAL AND IN VITRO STUDIES ON TOXICITY OF PVC

Agarwal *et al.*(1978) investigated the histopathological and biochemical changes in rat lung after a single intratracheal administration of 25 mg of respirable PVC dust (diameter<5mm). No significant difference was observed in the rate of mortality of control and PVC-administered rats. Inflammatory changes appeared in the terminal and respiratory bronchioles and alveoli. The cellular response to the presence of the dust in the lungs was in the form of cellular hyperplasia at the periphery of the dust masses. Alveoli contained macrophages laden with dust. In the neighbourhood of dust loci there were focal areas of interstitial fibrosis due to the proliferation of histiocytes and reticular fibers. Acute vascular changes with congestion of the blood vessels in the alveolar septa, leakage of erythrocytes, presence of edematous fluid in the alveolar walls or alveolar space, and haemosiderosis were also seen in this area. Encroachment of the dust masses by multinucleated cells was followed by the developing of granulomatous lesions. Later on the interalveolar septa were thickened and contained a network of fibers. After three months there seemed to be a tendency to clear out the entrapped dust.The activities of two energy-linked enzymes, succinic dehydrogenase (SDH) and adenosine triphosphatase (ATPase), and three lysosomal enzymes, acid phosphatase, beta-glucuronidase, and ribonuclease, were significantly increased in the early period and then started to decline. The activities of SDH and ATPase reached control values after 150 days, while those of the lysosomal enzymes remained significantly higher up to this period.

Srivastava *et al.*(1980) subjected rats to either one exposure to PVC dust (diameter 1.20 mm) in a concentration of 50-60 mg/m$^3$, for one hour or three exposures of one hour each on three successive days The animals were sacrificed either immediately after one and three exposures or after thirty days after three exposures. PVC dust was found deposited in the respiratory bronchioles and alveolar airspaces following one exposure. In lungs examined immediatly after three exposures, there was relatively greater accumulation of PVC dust with accompanying cellular proliferation. However, in lungs processed after 30 days following three exposures, the airspaces were generally cleared of the PVC dust. There was infiltration of PVC dust congregates in the lymphatics and in the epithelial layer of the bronchioles. They did not observe interstitial fibrosis and granulomatous lesions in the lungs.

Richards *et al.*(1981) let rats inhale a paste polymer PVC dust at an aerosol concentration (diameter 1.7 mm) of 10 mg/m$^3$ for 6 hr/day, 5 days/wk for a 15-wk period. There were forty exposed animals and forty controls with ten in each group being sacrificed at 3, 9 and 15 weeks after the start of exposure. The last groups were sacrificed 15 weeks after the end of exposure. They detected small, randomly scattered, lung lesions after 15 weeks of exposure. These lesions were characterised by

hypercellularity of the interstitium of the alveolar walls adjacent to areas of macrophage aggregates containing PVC. The changes persisted well after the end of exposure. The PVC-induced lesions showed only minimal increase in collagen and reticular fiber formation, with no evidence of extensive fibrotic reaction. Relatively few, if any, biochemical changes in PVC-exposed rats were detected at any exposure period either at the alveolar surface, the lung tissue, or other body organs. They concluded that at nuisance dust level this form of PVC polymer exhibits a weak biological reactivity, only detectable by histopathological examination.

Groth *et al.*(1981) exposed rats, guinea pigs and monkeys by inhalation (6 hr/day, 5 days/week) for up to 22 months to a 13 mg/m$^3$ concentration of PVC dust (diameter $<1.5$ mm). There were eighty exposed and eighty control rats, forty exposed and forty control guinea pigs that were sacrificed after 12 months, and ten exposed and ten control monkeys that were sacrificed after 22 months. Lung function tests were performed on monkeys before and after 9, 14 and 22 months of exposure. Aggregates of alveolar macrophages containing PVC particles were found in the lungs of all animals. These aggregates were more numerous in the monkey lungs. No fibrosis or significant cellular infiltrates were present in or near these cellular aggregates. No significant effects on pulmonary function could be demonstrated in the monkeys exposed to PVC. Under theconditions of this experiment, inhaled PVC produced a benign pneumoconiosis.

Wagner and Johnson (1981) exposed forty-eight rats to PVC dust (diameter 0.15 mm) at a concentration of 12 mg/m$^3$ for 7hr/day, 5 days/week, for 5 months. There were also 48 nonexposed controls. Six rats from each group were killed at the end of the exposure, and a further six a year after the start of the exposure. The remaining animals were allowed to survive until they died of natural causes. The PVC particles were present in the macrophages within the alveoli arising directly from the respiratory bronchioles immediately after the exposure. Occasional dust particles were observed in sections from the bronchopulmonary lymph glands, the Kupffer cells in the liver and in the spleen. At the end of a year, the dust was still present in the spleen and around some foci of macrophages there was evidence of a slight proliferation of reticulin fibers. This early dust reticulination did not show evidence of progression in any of the other animals, some of which survived for more than two years after the initial exposure So there was no indication of causation of significant pulmonary disease.

Takenaka *et al.* (1987) exposed groups of ten rats each, to titaniumdioxide (diameter 1.22 mm), PVC (diameter 1.31 mm) or iron powder (diameter 5.4 mm) at concentrations of 0, 3.2, 8 or 20 mg/m$^3$ for 8 months (5 hours/day, 5 days/week). After termination of the inhalation period, the rats were sacrificed for histopathological examination. There was dose-dependent accumulation of particle-laden macrophages throughout the alveolar region. There was interstitial inflammation of the lung with lymphoid hyperplasia in the lung associated lymph nodes. Granulomatous foci in the lung were also seen. The changes with PVC were more pronounced than for iron and titaniumdioxide. The authors postulated that the low bulk density and therefore higher number of particles inhaled at each dose may have contributed. Unfortunately there was no recovery period, the animals being sacrificed immediately at the end of the exposure period

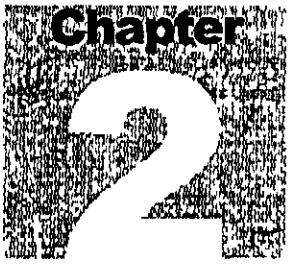
Frongia *et al.* (1974) exposed two guinea pigs and an unstated number of rats 24 hours a day, from two to seven months, to inhalation of PVC dust (diameter <1 mm) in the bagging area of a plant. There was a lack of adequate controls. In guinea pigs they found an initial alveolo-lobular macrophagic reaction, with multinucleated giant cells, and with very fine granules in the cytoplasm, wich were unchanged by usual coloring techniques. After longer exposure (seven months) granuloma-like foci were identified while the initial alveolar reaction was fading out. In rats there was much less alveolar reaction, but marked thickening of the septa due to histio-macrophagic infiltration was prominent; after seven months, the same granuloma-like changes as in guinea pigs became dominant.

Styles and Wilson (1973) measured the cytotoxicity of a variety of polymer dusts to suspensions of rat alveolar and peritoneal macrophages in culture by using trypan blue as an indicator of cell death. Suspensions of the same dusts were administered to rats by intraperitoneal injection and the tissue reaction examined at one and three months. Less than 2% of the peritoneal and less than 5% of the alveolar macrophages were killed following phagocytosis of dust. The dusts in this group were polyester powder, polyvinylchloride (Corvic, diameter 5-15 mm; Corvic ball milled: diameter 0.1-4 mm), polyethylene, polypropyleen, aragonite, alumina, agerite white, anthraquinone, kaolin, talc, magnesium trisilicate, carbon and Pelikan ink. One month after intraperitoneal injection ball milled PVC "Corvic" produced lesions, mainly involving macrophages, in which the material could be seen. These lesions resolved by three months. PVC "Corvic", anthraquinone, agerite white, Nonox D, magnesium trisiticate, polyethylene, carbon and Pelikan ink produced no lesions after intraperitoneal administration. A good correlation was found between the cytotoxicity of the dusts to macrophages in culture and the degree of fibrosis caused by them in the animals. The differences in cytotoxicity between dusts could not be related to concentration of dust, nor to differences in rates of phagocytosis, as dusts were generally ingested to the same extend.

Richards *et al.* (1975) reported on the high haemolytic potential exhibited by certain forms of PVC dust on human lung fibroblast cultures, because of the presence of a readily soluble, surface-associate agent.

Yu and Rappaport (1996) tested the validity of a Michaelis-Menten-like kinetic model of pulmonary clearance of insoluble dusts. Data were investigated from studies of pulmonary clearance in F344 rats exposed to antimony trioxide (Sb2O3), photocopy test toner, polyvinyl chloride powder (PVC), and diesel exhaust particles. The Michaelis-Menten-like model was used to develop a relation in which the pulmonary clearance half time was a linear function of lung burden. After combining all data, linear regression techniques were applied to investigate the underlying relations. With the estimated intercepts and slopes, the Michaelis-Menten-like kinetic parameters kmax (maximal clearance rate) and m1/2 (a characteristic lung burden at which kmax is reduced by 50%) were derived for the four dusts. The experimental data fit the linear regression very well (R2 = 0.989), suggesting that pulmonary clearance for the four dusts followed Michaelis-Menten-like kinetics. Values of the intercept terms were not significantly different among the four dusts (P = 0.294), indicating that the intrinsic clearance rates of F344 rats were the same among the four experiments. The intrinsic clearance half time was estimated to be 77.8 days, leading to an estimated kmax of 0.0089 day-1. However, the slopes of the linear relations were significantly different among the four dusts (P < 0.001). Values of m1/2 were ranked in the order of: Sb2O3 (0.69 mg) < photocopy test toner (0.97 mg) < diesel exhaust (2.49 mg) congruent to PVC (2.90 mg). This study suggests that the Michaelis-

Menten-like kinetic model reasonably describes the kinetic behavior of pulmonary clearance in F344 rats. The parameters m1/2 can be used to differentiate the potency of a particular dust for impairing pulmonary clearance.




# CASE STUDIES OF EFFECTS OF PVC DUST IN MAN

Arnaud *et al* (1978) and later Lazard et al. (1980), reported a 53-year-old man, who had been exposed for 23 years to PVC dust (mean diameter 1 5 mm) in the bagging area of a vinylchloride polymerisation plant that worked with the emulsion polymer method. The man, a smoker of 20-30 cigarettes a day since the age of 22, had a history of chronic productive morning cough for three years, and for three months he had noticed mild weakeness and slight exertional dyspnoea. He presented with a diffuse micronodular infiltrate on his chest radiograph. Light microscopy of lung biopsy showed a diffuse infiltration with histiocytes and multinucleated giant cells, with some collagen formation. Ultrastructural studies showed foreign particles in the macrophages, wich were identical with PVC powder viewed under the electron microscope. Incubation of PVC powder with human lung macrophages in vitro showed that the macrophages engulfed the powder to give a similar ultrastructural appearance. Clinically they found a slight reduction in vital capacity with no reduction in gas transfer factor, suggesting that the fibrosis was not as yet of much functional significance. Ten persons worked in the same conditions, but they had a normal pulmonary picture.

Hunter *et al.* (1981) reviewed the chest radiographs, physiology and lung histology of six PVC production workers, all of whom had been exposed also to the monomer (VCM). Three presented for investigation of radiological abnormality, one having been discovered in an epidemiological survey, and three had died of VCM induced liver disease. None had significant respiratory symptoms. Lung transfer factor was reduced in only one of the three with abnormal radiographs. All six lungs showed similar histological appearances, with an inflammatory interstitial infiltrate. PVC granules and other dust particles were demonstrated in the three in whom electron microscopy was performed.

Sulotto *et al.* (1985) described a 53-year-old man who worked in a PVC plant for 22 years; the last 13 years he worked as a dust mixer. The diagnosis was made on the basis of the histologic findings of a transbronchial biopsy, which revealed interstitial fibrosis with lymphoid cell, histiocyte and polynucleated giant cell infiltrates. The concomitant finding of liver aspecific portal fibrosis is of dubious interpretation since the patient had been exposed to several hepatotoxic substances (occupational and non-occupational) and traces of vinylchloride could also have been present in the working environment.

Antti-Poika *et al.* (1986) reported a case of a 43-year-old man who worked at a PVC factory and had an accumulated exposure to PVC of only about 750 days He had smoked one package of cigarettes daily for 20 years and suffered of a gradually increasing dyspnoea. Total dust concentration during

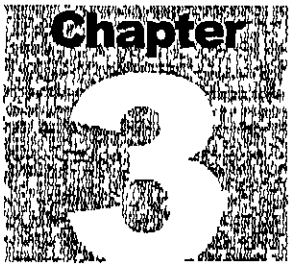
packing of PVC ranged from 0.3-42 mg/m$^3$ (median of 38 measurements 2 mg/m$^3$). He had been exposed to relatively low concentrations (0-3 ppm) of vinyl chloride monomer. Dust samples from the workroom examined by electron microscopy, revealed that most of the particles were smaller than 1 mm. The chest radiograph, the laboratory tests and the bone marrow aspirate were within normal limits. Spirometry yielded normal values but diffusing capacity transfer factor was abnormal. At biopsy there were PVC particles in the macrophages of the lung. Nevertheless, the causal association between PVC and the disease remains open. The report is interesting in that the exposures are more in line with the average appearance of facilities than those quoted in some of the other papers.

Lee *et al.* (1989) described a case of occupational asthma due to unheated PVC resin dust in a 32-year-old man who worked for 14 years in a factory manufacturing plastic seals for bottle caps. For the past eight years the patient worked in the mixing room where he was exposed to PVC resin dust and other chemicals during mixing. The mixture was made of PVC resin (a white powder that itself was a mixture of two emulsion resins with stabilisers added and one suspension resin without a stabiliser), dioctylphthalate or di-2-ethylhexylphthalate (DOP), a paste containing azodicarbonamide, colouring agent, and stabilisers. The pouring process was visibly dusty and took about 10 minutes six times a working shift. No local exhaust ventilation was provided. The other worker in the mixing room had no symptoms; one other worker had left 5 years previously with respiratory symptoms. The average concentrations of exposure to the respirable (<10 mm) and non-respirable dust were 0.16 mg/m$^3$ and 0.37 mg/m$^3$ respectively Chest x-ray examination did not show any evidence of pneumoconiosis. The patient had non-specific bronchial hyperreactivity as assessed by histamine inhalation challenge. A bronchial provocation test with 0.2 mg/m$^3$ respirable PVC resin dust for 20 minutes produced a fall in peak flow starting nine hours after exposure. It dropped to 58% of baseline at sixteen hours and the change was reversible with Ventolin No provocation test was done with the liquid DOP and the paste containing azodicarbonamide, the latter is known to induce asthma.

Studnicka *et al.* (1995) presented the case history of a 58 year old man who was exposed to thermoplastic dusts, mainly polyvinylchloride (PVC), for 10 years when he operated a plastic mill in a plastic reutilisation plant. He had smoked five cigarettes a day for 30 years. Radiography and high resolution computed tomographic scans of the lungs suggested both pneumoconiotic and scleroderma-like lesions. Transbronchial biopsy revealed foreign body granulomas with macrophages laden with birefringent inclusions which ultrastructurally resembled PVC dust. The lung function showed only a mild obstruction. Biopsy samples of thickened skin showed histological evidence of extensive fibrosis. During follow up Raynaud's phenomenon and oesophageal involvement developed The antinuclear antibody titre was 1:640, and the Sc1-70 subset was positive In the literature an association has been reported between systemic sclerosis and silica-induced pneumoconiosis, and between silica-associated scleroderma and Scl-70 auto-antibodies. One of the possible hypotheses to explain environmentally-induced sclerodermia is the presence of non-digestible particles within macrophages. These activated macrophages might stimulate fibroblasts in the lungs, and possibly the skin, to produce excess collagen by releasing growth factors. They concluded that exposure to PVC dust may cause pneumoconiosis and secondary systemic sclerosis.

White and Ehrlich (1997) described the case of a 35 year old man who during less than 10 years heavily exposure to PVC dust, developed dyspnoea and a mild restrictive lung disorder consistent

with PVC pneumoconiosis. He had never smoked, had no domestic bird exposure, no tuberculosis contact, nor any history suggestive of allergy or atopy. The chest radiography was normal but a high resolution computed tomographic scan showed a fine nodular pattern in both lower lobes, with no pleural or other pathology seen. Sarcoidosis could be excluded. Clinical and radiological abnormalities cleared within one year on removal from exposure, suggesting that in its early stages PVC pneumoconiosis is reversible.




# SURVEYS OF PVC WORKERS

## CHEST RADIOLOGY

A report by Vertkin *et al.* (1970) suggested diffuse pulmonary radiographic shadowing in 83% of 96 PVC workers, though no details of radiographic film reading methods were given.

Lilis *et al.* (1976; 1977) reported a high prevalence of radiographic abnormality in workers at two of three PVC plants in North America. They found small linear-reticular and/or nodular opacities in VC-PVC exposed workers. In evaluating the prevalence of the chest x-ray abnormalities two main trends could be identified. First, in the two groups, where there was a relatively high prevalence of such abnormalities, there was a statistically significant increase with duration of exposure. Second, the highest prevalence of chest x-ray changes was found in the plant with highest exposure levels, while the lowest prevalence characterised workers from the plant with known relatively low exposure levels. No dust measurements were reported, and although the radiographic appearances were recorded according to the ILO U/C pneumoconiosis classification (1971,1972) by five physicians experienced in this method, no information was given of reader agreement, nor are the criteria for "abnormality" given

Soutar *et al.* (1979; 1980; 1981) investigated in a cross-sectional survey, 818 men from the work force of a factory manufacturing PVC. The highest mean average respirable dust concentration for any occupation obtained over a shift by personal sampling carried out on 130 men, was 2.88 mg/m$^3$. The chest radiographs were read according to the ILO U/C classification. One of the three expert readers who examined the chest radiographs detected small rounded opacities (none greater than category 1/1) more commonly in the radiographs of men with higher exposures to PVC dust than in those with lower or no exposure. The other two readers did not detect an effect of PVC dust, though they saw small rounded opacities in a few cases. The opacities seen by these readers were not more common in those with higher exposure to dust than in those with lower or no exposure. Nevertheless, men with small rounded opacities also had reduced lung function, compared to those without.

Soutar *et al.* (1981) extended the sample of the study population mentioned above, to all other members of the current workforce. Four case/control studies were carried out on men selected from the original study population on the basis of radiological or lung functional abnormality where PVC dust exposure might have made an important contribution. All three readers recorded higher prevalences of small rounded opacities category 0/1 or greater on the second reading of the chest radiographies from the 818 men in the first study. These radiographies were also read twice within a

short time by a panel of five self-trained readers. The previous finding was confirmed, that estimated PVC dust exposure was related to abnormalities of the lungs demonstrated by the presence of small rounded opacities in the chest radiograph.

Mastrangelo *et al.* (1979; 1980; 1981) did an epidemiological study among 1216 workers, with no previous exposure to organic or inorganic dust, that were employed in PVC production factories. Of these 731 were exposed to PVC dust polymer alone and 485 had been exposed to monomer alone. In the drying, sacking and blending departments, PVC dust concentrations were over 10 mg/m$^3$ of total dust in about 60% of the samples, whereas in the polymerisation departments no concentration over 10 mg/m$^3$ was found. In the samples taken, particles with diameter of 1 mm to 6 mm constituted 4.5 to 30.9% of total dust weight. The chest x-ray films were read by two independent physicians utilising the ILO U/C pneumoconiosis classification. For statistical analysis, a consensus reading was used. In 20 subjects (1.6% of the total population; 2.7% of the PVC exposed group) they diagnosed a typical pneumoconiosis, i.e., chest x-ray changes (irregular opacities or frankly micronodular images) of at least class 1 profusion according to the ILO U/C classification Only two of them showed slight restrictive respiratory function impairments. They had all been exposed to high PVC dust levels. The mean age of this group was 44.9 years and the mean length of exposure was 11.6 years (none less than 5 years); 16 subjects were either smokers or ex-smokers. In 388 subjects (31.9%) they found slight chest x-ray alterations consisting of linear or irregular vanishing opacities, or both, classified as class 0/1 profusion; the remaining 808 subjects were class 0/0. The x-ray alterations were mainly related to age and smoking, and the role of exposure was minor.

Ng *et al.* (1991) studied 171 Chinese and Malay PVC compounding workers in comparison with an unexposed reference group of 48 workers from outside the plant. The highest exposed workers did not exceed 2.90 mg/m$^3$ (mean 1.55 mg/m$^3$) of respirable PVC dust. The previous dust levels were not known. Chest radiography was performed on the entire group of mixers (who were the most highly exposed to PVC dust) and subsamples of exposed nonmixers and unexposed referents. The x-rays were read independently according to the ILO U/C classification, by three readers who were not aware of the exposure status of the subjects to which the radiographs belonged. There was good reading agreement between the observers. Workers with high cumulative PVC dust exposure had a higher prevalence of radiological profusion of rounded and irregular small opacities Age, but not smoking, was significantly associated with radiological small opacities. It is difficult to exclude the possibility that the radiological opacities could also have resulted from additives containing radiodens calcium and barium compounds in the mixture. The effects of ageing and cigarette smoking were unlikely to produce radiological opacities more profuse than category 1/0. There should therefore be little doubt that the radiological profusion 1/1 in five workers indeed represented PVC pneumoconiosis. This report stands up well to assessment against the I.R.L.G. guidelines (1981) for the reporting of epidemiology studies. The indications are that it was well conceived and a well conducted study. The reported effects are larger than those in other studies, the response to the symptoms questionnaire are different and the radiological findings are different. Nonetheless the various tests seem to have been carried out in valid manner, and the analyses are appropriate. The study suffers from the defect of all cross-sectional studies in as much as the pulmonary status of the groups could have been different when taking up employment and the observed differences may not be attributable to occupational exposure. The analysis is different to that used by the I.O.M. team (Soutar *et al.*, 1979). The categorisation of exposure into high and low is tantamount to a division into oil mixers and others, this must have made the analysis more difficult because it creates

unwanted correlations. Any criticism of this paper can only be at the second order of importance. There appear to be no fundamental flaws. It is interesting that the excess of wheezing has been found by a question added to the MRC questionnaire, and it is strange that the radiological findings should differ from those in the I.O.M. study.

# LUNG FUNCTION

Miller *et al.* (1975; 1980) and Lilis *et al.* (1976; 1977) reported a relatively high prevalence of obstructive changes. $FEV_1/FVC$ was reduced (<75%) in about 45% of all examined workers in the two PVC plants in North America mentioned above An attempt to evaluate possible correlations between chest x-ray changes and pulmonary function did not show any consistent link Airway obstruction correlated with age and duration of exposure to VC-PVC. It is conceivable that chest x-ray changes and obstructive pulmonary function abnormalities reflect different pathologic processes, the chest x-ray changes being mainly related to parenchymal damage, while the obstructive pulmonary function changes would reflect airway changes. There wasn't an adequate control group included in the studies.

Soutar *et al.* (1979, 1980; 1981) found that the $FEV_1$ was statistically significant lower among men with higher PVC dust exposure. This effect was seen principally in current cigarette smokers, and not confirmed among non-smokers when considered seperately. The pattern of results suggested that there were real differences in the response to PVC dust related to smoking habit. The magnitude of this reduction in all men in relation to the mean dust exposure was approximately one-seventh of that caused by ageing, and of a similar magnitude to the loss caused by smoking 20 cigarettes a day. The FVC was also statistically significant reduced at higher PVC dust levels. The magnitude of this reduction was less than that of the $FEV_1$. The $FEV_1/FVC$ ratio and the TLco were not significantly related to PVC dust exposure.

Lloyd *et al.* (1982, 1984) investigated a report that some men from a PVC factory had abnormally low carbon monoxide diffusing capacity. Respiratory function in 265 present and past employees was compared to that of 219 workers from a nearby foundry. Overall there was no difference in the groups. Cases were then selected on the basis of TLco measurements and a nested case control study was carried out. There was an excess of cases in the PVC group exposed before 1975 when levels of concurrent VC exposure were said to be much higher. No such effect was seen in foundry workers employed prior to 1975. The study concluded that current exposure to PVC dust had any effect on lung function. No data on PVC or VC exposures were presented. The validity of the foundry group as a control was not discussed.

Chivers *et al.* (1980) studied three groups, a PVC dust group, a solvent exposed group, and a mixed group. The PVC dust group was 104, the solvent group 112, and the mixed group 293. Static monitoring results only were available and these only for the previous two years . Exposure durations were rather short, the mean being only seven years in the PVC exposed group. Only 11 PVC exposed workers had more than fifteen years service. No significant PVC dust exposure related effects were found. Smoking was shown to be the dominant cause of reduced lung function.

Magnavita *et al.* (1983) followed 79 exposed workers and 25 clerical workers as a control group, in a longitudinal study in a PVC-compounds factory. In the exposed group several ventilatory changes,

mainly bronchiolar obstruction, were disclosed. The prevalence of these changes increased from 12.00% in 1976 to 35.44% in 1981; the incidence was about 6%. Controls had only one impaired case in 1976, and they did not show any new case until 1981. The difference between prevalence rates was highly significant. The PVC exposition of the workers was low (< 1mg/m$^3$; 95% of the particles had a diameter < 5 mm) but they had been exposed to very high VCM concentrations in the past (> 50 ppm). The workers were also exposed to aerosols containing phthalates and thermal degradation products of the used resin.

Baser *et al.* (1985) looked at pre and post shift lung function in 174 subjects spread over five departments of a calendering plant of which three were subjectively free of exposure to dust, vapour or fume. The PVC dust levels were not measured in the plant under study, but there was said that they were low. No differences were apparent between exposed and non-exposed groups There was however a lenght of service effect for the factory as a whole with no difference between exposed and non-exposed groups. Thermal degradation products in calendering were the potential exposure rather than PVC dust. Selection bias would have been an equally plausible explanation of the results.

Siracusa *et al.* (1984; 1988) and Volpi *et al.* (1986) studied between 1973 and 1984 the lung function in a group of 126 workers; 29 of them were exposed to PVC only (in 10 samples: 3.3 mg/m$^3$ as geometric mean and a range of 0.9-16.1 mg/m$^3$), PVC plus light exposure to asbestos cement, and asbestos cement only (up to 147.0 mg/m$^3$ static sampling). They gave no information about the diameter of the PVC particles. After adjustment for age, height, and smoking status at the date of first employment, the decline in FVC and $FEV_1$ among the nonsmokers-light smokers was slightly accelerated with lenght of employment in the PVC dust exposed group. The heavy smokers had FVC and $FEV_1$ predicted values that were lower than those of the nonsmokers-light smokers; these differences remained constant with length of employment. So the negative effect of smoking habits was additive with PVC exposure.

Ernst *et al.* (1988) compared 70 workers in a PVC fabrication plant to 48 in a vegetable packing facility. The average age of the PVC workers was 6 years more than the controls and they also smoked more. $FEV_1$/FVC was significantly lower in the PVC workers. Cross-shift drops in $V_{max75}$ of 15% or more were also more prevalent in the exposed group. When examining the association between months of work within the exposed group and spirometric indices of airway obstruction, no relationship could be demonstrated. However, an inverse dose-response relationship was seen between level of FVC and duration of employment, suggesting a restrictive impairment. Historical exposures were not available but current PVC dust exposures were very high at 21 mg/m$^3$. Exposures to plasticisers (phthalic anhydride and trimellitic anhydride, two recognised causes of occupational asthma) and thermal decomposition products were probably insignificant compared to the PVC dust. While the specific exposures have not been identified, it appeared that employment in PVC fabrication may be associated with both obstructive and restrictive ventilatory effects. The more prominent obstructive results in this study, as compared to those of Baser *et al.*(1985), might be related to differences in the intensity of exposure to PVC dust.

Nielsen *et al.* (1989) compared 20 workers in a PVC processing plant to 19 unexposed workers. The PVC workers were exposed to PVC thermal degradation products (PTDP) and phthalic acid esters (PAE; up to 2 mg/m$^3$). No significant differences were found between exposed and control subjects with regards to spirometry or volume of trapped gas before or after choline inhalation.

Ng *et al* (1991) found an association between PVC exposure and a restrictive type of lung function impairment The average lung function loss was modest; both $FEV_1$ and FVC were about 4% lower in the low-exposure group and 7% lower in the high-exposure group.

Lee *et al.* (1991) studied the diurnal variation in peak expiratory flow rate (PEFR) in 24 mixers and 24 non-mixers in three PVC compounding plants, and 24 non-PVC controls. All the groups were matched for age, race and smoking. The mean respirable dust concentration (essentially PVC dust) was 1.6 $mg/m^3$ for mixers and 0.4 $mg/m^3$ for non-mixers. The mean diurnal variation in PEFR of the mixers was 6.5%, and 4.8% for non-mixers and 4 3% for the non-PVC controls $FEV_1$ for the mixers was 10% below the predicted values, whereas that of non-PVC workers was 2% below predicted values. Twenty nine per cent of mixers complained of wheezing compared with 4% of non-mixers and none among non-PVC workers. This study is very similar to the one by Ng *et al.* (1991). Strangely neither paper refers to the other The exposed groups are almost identical in the two studies, but the control groups are completely different. Quite why the totality of the exercise was conducted and reported in this way is not clear. Qualitatively the results in the two papers are quite similar and most of the comments on the paper of Ng *et al.* (1991) apply equally to this paper. PEFR is usually used as a diagnostic tool for asthma rather than as a mean of obtaining quantitatively precise data. The difference between the mean diurnal PEFR of the mixers and the non-mixers is of questionable significance.

# RESPIRATORY SYMPTOMS

Lilis *et al.* (1976) reported high prevalences of chronic bronchitis among PVC workers, using standard questionnaires (20%), but it was not clear to what extent this was due to smoking and local atmospheric pollution.

Vertkin *et al.* (1970) found a lower prevalence of cough (7%), but the method of questioning was not described

Soutar *et al* (1979; 1981) found a relationship between exposure to PVC dust and the complaint of slight exertional dyspnea, but this relationship was seen only in cigarette smokers and not in non- or ex-smokers. They concluded that it was unlikely that exposure to PVC dust at these levels had caused serious respiratory disability, though the possibility of a rare idiosyncratic response to the dust could not be excluded

Soutar and Gauld (1983) did a follow up study of 28 men identified as having small rounded opacities on chest x-ray, compared to 29 controls. Lung function was only trivially less in the study group Symptoms of mucus hypersecretion were also increased and there was a suggestion that the physical sign of late inspiratory crackles was increased in the study group. They went to examine a further 13 smokers and 18 non-smokers with high exposure. The conclusion was that the x-ray appearances were not associated with important functional effects or clinical illness.

Nielsen *et al.* (1989) found more symptoms of unspecific bronchial hyperreactivity in the exposed group. The exposed had more symptoms from eyes and upper airways than the controls.

Chapter 4

# DISCUSSION

## DEFINITIONS

Nuisance dusts are, according to the ACGIH, those having on lung tissues reactions with the following characteristics:

1. The architecture of the air spaces is not modified,
2. Collagen (scar tissue) is not formed to a significant extent,
3. The tissue reaction is potentially reversible.

Physical irritants without evidence of significant risk of deleterious lung or systemic effects are within this category for which ACGIH and OSHA apply a generic limit

The term "inert" dust is considered by ACGIH as inappropriate because there is no dust that doesn't evoke some cellular response in the lung when inhaled in sufficient amounts. **Instead of inert dust the term "nuisance" dust is used in this document.**

Adverse health effect is considered as a measurable structural, functional, or biochemical antagonistic change in health parameters.

## TOXICOLOGY

Inhalation of PVC dust at 10 mg/m$^3$ produces an effect in the rat lung similar to that produced by a range of insoluble nuisance dusts, namely aggregates of dust containing alveolar macrophages with minimal associated fibrotic response. Qualitatively similar changes were seen in the guinea pig and monkey. Pathology from one of the cases of alleged human pneumoconiosis due to PVC dust show the identical build up of PVC dust particals in the lung to that seen in the other species studied. There is thus good agreement between all the species tested giving confidence to the adequacy of the models examined. Turning to quantative considerations species differences in the anatomy of the head and upper airways influence initial deposition patterns but much less the long term retention and fate of inhaled material. Deposition patterns are also influenced by respiratory parameters such as respiratory rate and tidal volume. Metabolic rate is inversely related to body size, and smaller animals have higher minute respiratory volumes per unit body mass. This means that they inhale

larger amounts of aerosol per unit body mass than larger animals or humans (Mc Mahon *et al.*, 1977, Leith, 1984).

The nature of PVC dust is such that significant dissolution would not be expected. Two clearance mechanisms would be expected One would be by physical translocation via the mucociliar escalator and the other direct to the lung-associated lymph nodes. Thus in workers there could be expected to be two rates of clearance From the upper airways clearance would be reasonably rapid but from the alveolar region it would be very slow. For single exposures the net retention and clearance patterns for pulmonary burdens of solid aerosols have been studied by Snipes (Snipes, 1989). Rats appear to clear material more rapidly and with a different pattern However if exposure is prolonged but still below that expected to produce overload (i e. equilibrium could not be reached) the only effect that this would have is to make the attainment of equilibrium in terms of lung tissue burden more quickly. Differences in equilibrium concentrations then appear to be dominated by the effects of different airway dynamics. Consideration of the relative dosimetry between rats and humans for this 'point of contact' effect suggests that the human could be expected to retain within one order of magnitude the same number of particles from an equivalent exposure. Allowing for the different airway dynamics, obligate nose breathing in the rat and the nature of the effect the rat could be expected to only slightly overestimate the human hazard if at all and this would appear to be confirmed by the limited information from monkeys. Snipes (1989) has computed the accumulation of particles in lung with chronic exposures to concentration of particles projected to produce the same lung burden in laboratory animals and humans He estimated that exposure for 8hrs/day, 5days/week, to 0.50 mg/m$^3$ dust (density 1 g/ml, 1 mm mass median diameter) would produce a lung burden of 0.32 mg/g lung tissue in humans after two years. The same lung burden would be produced under the same conditions after exposure to 0.26 mg/m$^3$, 0.10 mg/m$^3$, and 0 76 mg/m$^3$ respectively for monkeys, guinea pigs, and rats. None of these concentrations would be expected to result in overload as demonstrated by the attainment of equilibrium.

Considering all the above the monkey would appear to the best species in this case on which to base quantitative comparisons with likely human effects. The overall clearance rates could be effected by concomitant exposure to a range of non-specific bronchial irritants, the commonest being cigarette smoke.

Although insoluble nuisance dusts produce qualitatively similar effects on the lung, quantitative differences can arise purely as a consequence of their varying physical properties. In the case of PVC the lower bulk density can give a misleading impression of greater potency when the dose is expressed gravimetrically and the effect is likely to be related to the number of particles inhaled.

It was noted that the tests carried out had used emulsion PVC rather than suspension PVC. The main difference in vivo between the PVC dust from these two production methods is probably the different particle size For suspension PVC 90% of the particles are greater than 5 mm but for emulsion PVC 100% of the particles are less than 0.8 mm although some conglomeration occurs (Casula *et al.*, 1977).

# EPIDEMIOLOGY (General)

The references reviewed contain little data on historical exposures. Where attemps have been made to measure current exposure estimates are variable with some evidence of high exposure. Exposures reported have generally been in the range of 7-15 years which falls short of a full working lifetime of say 30 years. On the other hand it must be said that most other non-malignant dust related lung diseases would have been detected in this period. This is presumably an indication that any possible effects will not be severe. The effect of formulation additives is difficult to assess. The reported populations will all have been exposed to a range of other compounds which could have had an effect in their own right or have contributed to a small effect of PVC dust itself. On the other hand the observed effects are entirely consistent with what would be expected from the toxicology of PVC dust.

# X-RAY FINDINGS

Taken overall there does seem to be a relationship between exposures to PVC dust and small rounded opacities on x-ray. The confounding factors of smoking and age add to the difficulty of interpretation. The nature of the appearances are consistent with that seen in high exposure to other insoluble nuisance dusts. Changes generally seen are at ILO classification 1 or less. Occasional cases have been reported with more marked findings. These presumably relate to higher exposures.

# LUNG FUNCTION

A range of symptomatic, obstructive and restrictive deficits are reported, apparently without a clear-cut pattern In view of the nature of the likely pathology and the small magnitude of effects generally reported this is not entirely unexpected. The effects appear to be more marked in smokers which would be consistent with their likely impaired clearance. The effects of cumulative dust exposure, tobacco smoke exposure, and age can all be expected to be correlated and this makes interpretation difficult. In all but a few cases the magnitude of effect is small.

Ng *et al.* (1991) couldn't find an increased prevalence of dyspnea, but they reported an increasing prevalence of wheezing or chest tightness. Reversible airways obstruction was possible.

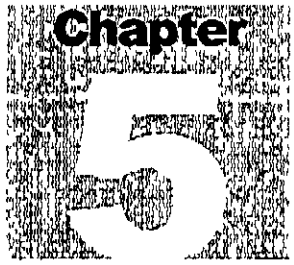
# FACTORS OTHER THAN PVC DUST EFFECTS

Lilis *et al.* (1976, 1977) found that the prevalence of positive smoking history in workers with abnormal chest x-ray films was statistically significant higher in both groups of PVC workers. This could indicate a multiple factor effect of smoking and VC-PVC exposure.

Miller (1975) reported for the same group of workers that the high prevalence of impaired flow (57.5%) could not be attributed to smoking. Prevalence in nonsmokers was 36 4% when exposure was less than 10 yr, 42% when exposure was between 10 and 20 yr, and 80% when exposure exceeded 20 yr. The last was virtually the same rate as for smokers exposed more than 20 years. The same trend was shown with increasing age. Unlike younger workers, when smokers and nonsmokers age 40 years and older are compared, prevalence rates of air flow impairment are not statistically different. These findings suggest that occupational or other environmental factors were operative. Age seemed not to be an important factor in the appearance of small linear-reticular or rounded opacities in VC-PVC exposed workers

Soutar *et al.* (1981) found that the prevalence of small rounded opacities category 0/1 or greater, recorded by all three readers were related to age. The deterioration in lung function was also strongly associated with age. Cough, sputum and other respiratory symptoms were strongly related to smoking habits. So also were abnormalities of lung function.

Nielsen *et al.* (1989) found that one exposed subject had a significantly raised level of IgG against phthalic anhydride, indicating that sensitisation can occur in PVC processing.




# CONCLUSION

The data reviewed do not represent conclusive evidence of an adverse effect. Rather the data from a number of sources is indicative of a small effect which is entirely consistent with what would be expected from exposure to an insoluble nuisance dust. Two individual case reports indicate more severe effects but these have presumably been related to very high exposures.

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