EXPOSURE PROFILES AND PULMONARY RESPONSES IN QUEBEC CHRYSOTILE ASBESTOS WORKERS

by

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Statement of originality

Asbestos exposure may be followed by various non-malignant changes in the respiratory system; relationships between exposure and these changes have been convincingly demonstrated in several independent studies. However in general, data have not delineated a single exposure-response relationship but have been compatible with a range of such relationships. This may in part be due to the fact that studies have used different approaches to the problems of operationalizing exposure as well as responses.

Commonly used indices of exposure include duration (years of exposure, years since first exposure) as well as cumulative exposure (the sum of the cross products of exposure level and duration). However it is conceivable that measures other than the simple summation of annual dust exposures would show a stronger relationship to response. In other words the profile of exposure may be important, yet this feature has received little attention in studies reported to date.

The present study used data on exposure (job history, environmental levels and work records) and respiratory responses (radiologic, assessment, symptoms and lung function) gathered in a previous prevalence study in Quebec asbestos workers. Its originality is 1) in the operationalization of indices to take into account various exposure profiles 2) the operationalization of the response to correspond to clinical entities and 3) the exploration of their interelationships. It shbuld be noted that as observations were not originally made in SI units and no reliable conversion factor exists, all observations and results in this research are reported in the original units.

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ABSTRACT

The objective of this study was to investigate the influence of the temporal pattern of asbestos exposure on subsequent respiratory tract changes. A cohort of 983 male Quebec asbestos miners and millers who were still working in 1966 was identified. Data were available on the men's latest chest x-ray, their responses on the MRC respiratory symptom questionnaire, and their pulmonary function test results. Estimates of annual dust exposure for each subject were available, based on environmental measurements made since 1948 and on extrapolations before that date. Factor analysis was used to develop several indices of respiratory morbidity that could be conceptualized in clinical terms. The relationship of these indices to cumulative dust exposure as well as to several dust variables which described the profile of dust exposure was then explored using regression analyses. The men's ages and smoking status were taken into account. Several descriptors of the temporal pattern of exposure were found to be related to subsequent response. These varied across the response scales, with earlier dust exposures tending to have more effect for long term processes, such as fibrosis and bronchitis, and more recent exposures tending to have more effect on the more acute airway responses. In the case of airways reactivity both early and recent exposures are important. Exposure-response relationships for pleural disease seem less clear than for parenchymal disease.

Résumé

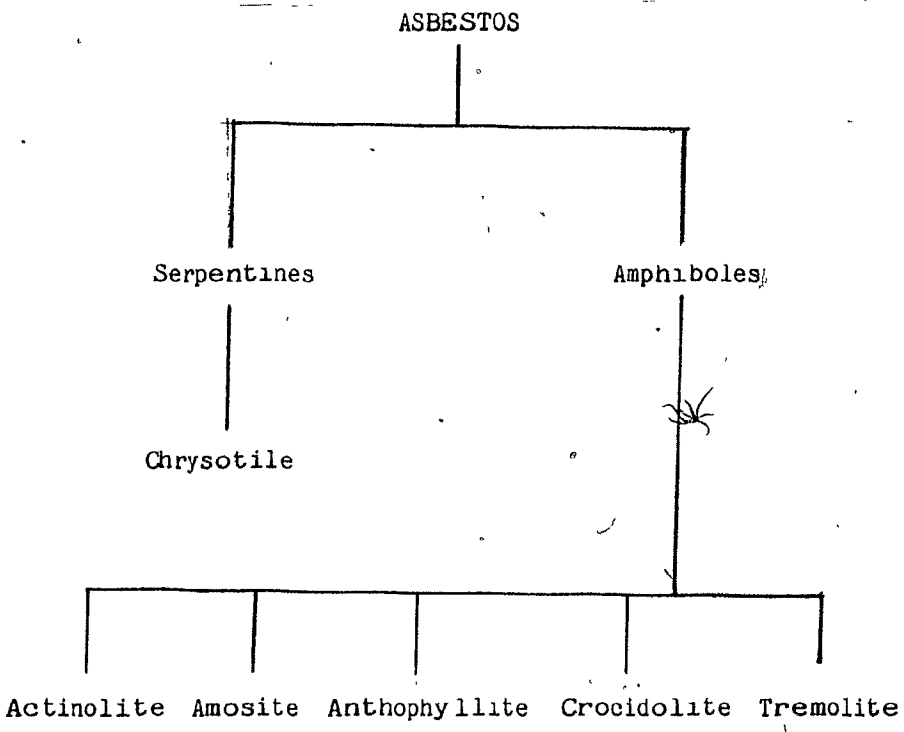
Le but de cette étude était d'examiner l'influence des caractéristiques temporelles de l'exposition à l'amiante sur des changements ultérieurs du système respiratoire. Neuf cent quatre-vingt-trois travailleurs des mines et moulins d'amiante chrysotile de la province de Québec qui travaillaient en 1966 ont été identifiés. Pour chaque sujet des informations étaient disponibles sur sa radiographie pulmonaire la plus récente, ses réponses à un questionnaire sur les symptômes respiratoires, et les résultats de ses examens de fonction pulmonaire. De plus pour chacun d'entre eux, un indice de l'exposition annuelle à la poussière d'amiante avait déjà été calculé en se basant sur des mesures environnementales faites depuis 1948 et sur des extrapolations pour les années précédentes. Plusieurs indices de morbidité respiratoire ont été élaborés. Les relations entre ces indices et l'exposition cumulative à la poussière d'amiante ainsi que certaines variables reflétant les caractéristiques temporelles ont été examinées en utilisant des analyses de régression. L'âge de chaque sujet et le nombre de cigarettes fumées quotidiennement ont été pris en ligne de compte. Des relations entre plusieurs paramètres décrivant les caractéristiques temporelles d'exposition et les réponses respiratoires ont été trouvées. L'exposition à la poussière d'amiante ayant eu lieu peu de temps après qu'un sujet ait commencé son emploi était importante pour des processus à long terme, par exemple la fibrose et la bronchite, tandis que l'exposition récente avait de l'importance pour les réponses aigues des voies aériennes.

INTRODUCTION

1.1 Asbestos Types, Distribution, and Uses

The word asbestos is derived from the Greek, meaning incombustible. It refers to a group of silicate mineral fibers. The fibers are divided into serpentine and amphiboles, depending on fiber configuration. Serpentine, as its name suggests, is curved and amphibole is straight. There are several commercial amphiboles but one main serpentine.

Figure 1 Main types of asbestos (38)



Macroscopic differences in the shape of serpentine and amphibole asbestos are paralleled by differences in chemical composition and in physical properties.

Chrysotile asbestos is composed of alternating silicate and brucite layers. The silicate layer consists of planar linked silica tetrahedra in a pseudo-hexagonal arrangement. The brucite layer consists of ionic magnesium octahedrally coordinated with hydroxyl groups and oxygen. The chemical formula of chrysotile is $X_6(Si_4O_{10})(OH.O,F,Cl)_8$ (38). The X position is most commonly filled by Mg, but trace amounts of Fe, Ni, and Mn may also be present. The surface of chrysotile is usually hydrophilic, thus particles are water soluble. The net electrostatic charge in aqueous solution is determined by the hydroxyl groups surronding the magnesium ion. Single chrysotile fibers are usually hollow tubes with a central capillary, although fibrils without a central capillary have also been found. The internal diameter of a fibril is in the range of 20-30 nm and the outer up to 600 nm. Dimensions may vary from deposit to deposit. Canadian fibrils tend to be somewhat larger than others.

The amphibole types of asbestos are double-chain inosilicates, cross-linked by cations. In all cases fibrils are straight rather than curved. General chemical formulae are given in Table 1.

Table 1 Amphibole Asbestos Formulae(38)

Anthophyllite	$-(FeMg_6)Si_8O_{22}(OH)_2$
Amosite	$-(Fe_6Mg)Si_8O_{22}(OH)_2$
Actinolite	$-Ca_2(MgFe_6)Si_8O_{22}(OH)_2$
Tremolite	$-Ca_2(Mg_6Fe)Si_8O_{22}(OH)_2$
Crocidolite	$-Na(Fe_2^{3+}Fe_3^{2+})Si_8O_{22}(OH)_2$

All types of asbestos are related to either serpentine or amphibole minerals which may form fibres similar to asbestos. Amphibole minerals in particular are quite abundant, making up 8% of the earth's crust.

Asbestos has been mined commercially for over 100 years. Currently, the world's largest producers are the U.S.S.R., Canada, and South Africa. Small deposits have been mined on every continent. World production has increased from 2,210 million kilograms in 1960 to 5,178 million kilograms in 1976. In 1960 Canada accounted for 45% of the world production and the U.S.S.R. for 29%. In 1976 these percentages were reversed (38).

Asbestos production has kept pace with the increasing number of uses that have been found for it. These uses now number in the thousands. Applications in the construction industry account for the largest share of asbestos production. These uses include asbestos cement sheets and pipes, floor and ceiling materials, and insulation of all sorts. Friction linings, including brakes and clutches, are another important

use of asbestos. The potential hazard of asbestos in various settings depends on whether it is "locked-in" to a matrix or whether it can be freely dispersed into the environment (38, 62). Use of asbestos in cement pipes may not entail as much of a hazard as the use of asbestos as a spray-on compound for fire-proofing.

1.2 Health Effects of Asbestos

1.2.1 History

It was approximately twenty years after the start of commercial asbestos mining in Quebec in the 1880s that the first case of asbestosis was reported in Great Britain by Murray (61). Another thirty years passed before the causal link between asbestos exposure and the development of diffuse interstitial fibrosis was generally accepted. In 1930 the report of Merewether and Price led to recommendations for environmental controls (57).

Five years later, in 1935, the first case of lung cancer associated with asbestos exposure was reported by Lynch and Smith (53). It was 20 years later that Doll (19) concluded that asbestos workers had 10 times the risk of developing lung cancer as did the general population.

The report of an association between a second malignancy, mesothelioma, and asbestos came in 1960 (83). Unlike previously reported cases of asbestos related disease, some of

the people affected by this disease had no occupational exposure to asbestos. Their exposure consisted of having lived in communities close to asbestos mines, or in sharing homes with asbestos workers.

In general, with the passage of time, more and more health hazards of asbestos exposure have been recognized. A review by Becklake in 1976 (8) contained the following table of pathologic effects and the status of their association with asbestos.

Table 2 Health effects of asbestos

Site of Effect	Effect	Association
Respiratory Tract		
Larynx	carcinoma	possible
Lungs	asbestos bodies	established
	diffuse interstitial fibrosis	established
	bronchial carcinoma	co-factor with cigarettes
Pleura	hyaline plaques and calcification	established
	malignant mesothelioma	established
	pleural effusion	established
	asbestos corns	established

Peritoneum		
	malignant mesothelioma	established
G. I. Tract		
	neoplasia	established
Ovary		
	carcinoma	remotely possible
Breast		
	carcinoma	remotely possible

As the above table shows, the effects of asbestos can involve a variety of organ systems, foremost among them is the respiratory system. Asbestos related changes of the respiratory system may be divided into neoplastic and non-neoplastic processes. Recent literature has in general been more concerned with asbestos related neoplasms than with non-neoplastic asbestos induced disease. Part of the reason for this may be that asbestos was shown to cause lung fibrosis long before it was implicated as a carcinogen. Another reason may be the tendency to focus on mortality rather than morbidity as outcome. Several studies in the last 15 years have dealt extensively with the risk of developing respiratory malignancies in various groups of workers exposed to asbestos (49,58,65,83). As this study is concerned only with non-neoplastic disease, further sections will deal only with non-neoplastic effects of asbestos.

1.2.2 Parenchymal Fibrosis

1.2.2.1 Definition

Asbestosis is a fibrotic response of the lung to the inhalation of dust containing asbestos particles.

1.2.2.2 Gross Pathology

The appearance of lungs affected with asbestosis is dependent on the severity of the disease(15a). Initially the lung size is normal, but with increasing extent the lung size decreases. In early stages, lesions tend to be peribronchiolar and concentrated in location. The fibrosis may extend into the intralobular septae. Eventually areas of fine, grayish fibrosis coalesce into an extensive fibrotic network. This network of fibrosis may parallel the pulmonary lobules. Generally, the lower lobes are affected first and more severely. Lung sections with asbestosis feel stiff to palpation. The more severely affected lungs feel relatively heavy due to the fibrosis, despite their reduced size. Later changes include bronchiectasis and emphysema. It is unsure whether these changes are part of the asbestotic process or whether they are due to concurrent smoking exposure and chronic bronchitis. Cystic lesions 1-3 mm in diameter have been reported and named "honey-comb" lung. These cysts are located between areas of fibrosis, but generally are not that extensive (36).

1.2.2.3 Microscopic Pathology

The basic lesion in asbestosis is a diffuse peribronchiolar fibrosis. Microscopically, initial signs of change may be concentrated at the level of the respiratory bronchiole. These changes may triggered by the deposition of dust and the accumulation of macrophages and reticular fibers. The earliest reaction may be a desquamative response in the alveoli or alveolitis. From the initially affected areas the process extends to adjacent alveoli. The peribronchiolar fibrosis progresses to involve the interstitium giving rise to a diffuse fibrosis, which may result in areas of fibrosis.

Asbestos bodies may be expected to be present in asbestotic lungs. These are asbestos fibers coated with mucoprotein. They may be seen under light microscopy and may range up to 250 um in length, the diameter is usually 2-5 um (14). They may be located in the alveolar or bronchiolar spaces or within lung tissue. Asbestos bodies are probably formed by the engulfment of an asbestos fiber by a macrophage (14). Asbestos bodies have been the topic of some controversy and since other fibrous particles may lead to the formation of similar bodies, the term ferruginous body is prefered by some to describe the mucoprotein covered fibers that may be seen on light microscopy. This would reserve the term asbestos body for those bodies in which the core has been positively identified as an asbestos fiber (31). The presence of asbestos

bodies in the lung or in the sputum does not imply that fibrosis is present or will follow. They merely serve as a marker of asbestos exposure, occupational or otherwise.

A classification scheme for grading the severity and extent of asbestosis has been developed (35).

Table 3 Grading of Asbestosis

Extent A - None

B - Less than 25% of the lung substance is involved

C - 25-50% of the lung affected

D - More than 50% of the lung affected

Severity 0 - None

1 - The lesions consist of slight focal fibrosis around respiratory bronchioles associated with the presence of asbestos bodies

2 - Lesions are confined to respiratory bronchioles of scattered acini. Fibrosis extends to alveolar ducts and atria as well as to the walls of adjacent air sacs.

3 - There is a further increase and condensation of the peribronchiolar fibrosis with early widespread interstitial fibrosis.

4 - Few alveoli are recognizable in the widespread diffuse fibrosis, bronchioli are distorted.

A more recent classification may be found in Craighead et al(15a).

1.2.2.4 Clinical and Laboratory Findings

When the possibility of asbestos related disease is considered, a history of past exposure must be obtained. For many patients this is readily elicited. However, others may not recall exposure unless detailed questioning is carried out. Yet others may not realize that they have been exposed to asbestos, for these people a detailed work history may be the only means of surmising previous exposure. A complete history may also allow a crude quantitative estimate of exposure.

Initial clinical presentation may consist of dyspnea associated with fine end-inspiratory crackles at the lung bases. Dyspnea is generally progressive, occurring at first only on exertion and then noticable when prgressively less effort is expended. Along with the increase in severity of symptoms, the crepitations generally involve a larger part of the lungfields and are heard during part of the inspiratory phase. While cough, either productive or non-productive, may also be found in asbestosis, the significance attributed to this complaint varies (8,77). Becklake states that the symptom often cannot be attributed to differences in smoking habits, and feels that the symptom may relate to asbestos exposure. Selikoff and Lee state that cough is only prominent in cigarette smokers and caution that cough in a non-smoking asbestos worker must arouse suspicion of infection or malignancy. Pain may also be present, usually in the lower

chest region. The etiology of this also seems to be disputed with either muscle (8) or pleura (77, p.151) given as the site of origin. Clubbing and cyanosis may also be present, but may be due to other causes. When clubbing is due to asbestosis it is not necessarily indicative of extensive disease.

Lung function changes of varying severity are found in asbestosis. Certain changes may precede radiologic detection of disease (37). The fibrosis due to asbestos is generally believed to produce a restrictive function pattern. However, an obstructive pattern of change is also seen in a number of subjects with asbestosis. Presumably the restriction is produced by interstitial fibrosis and the obstruction may be the consequence of peribronchiolar fibrosis if this is extensive. So far, an association between large airway abnormality and/or air flow limitation and asbestos dust exposure has not been conclusively demonstrated. While restrictive changes are more common than obstructive ones, an appreciable number of workers have been shown to have obstructive, or mixed obstructive-restrictive changes in their pulmonary function tests (26). Initial pulmonary function change may consist of a reduction in carbon monoxide diffusion capacity. Later changes typical of restrictive disease include a reduction in forced vital capacity (FVC) and 1-second forced expiratory volume (FEV_1). These measures are decreased to roughly the same degree, so that the ratio FEV_1/FVC is preserved. There may be a lesser reduction in residual volume (RV).

Radiographic changes found in asbestosis may not be noticed until the disease has advanced to the point where pulmonary function test changes and even dyspneic symptoms are already present (77, pp.152-158). As with physical findings, the first changes are usually at the lower lung. Radiologic changes indicative of parenchymal disease are non-specific and similar radiographic changes are found in any interstitial fibrosis. The initial change is usually a fine reticular pattern developing in both lower lung fields. The presence of pleural changes typical of asbestos exposure may be the clue as to the etiology of the parenchymal changes.

Later changes in parenchymal disease include irregular or rounded small opacities. Rounded opacities are more typical of silicosis than asbestosis but may also be found in workers with only asbestos exposure. In addition to opacities, other changes have been described and include a diffuse haze (ground glass appearance), septal lines, ring shadows (honey-combing), and hair line shadows.

The ILO U/C classification scheme has been constructed to allow grading of both the parenchymal and the pleural changes found in pneumoconioses (39). The development of this descriptive scheme has improved diagnostic as well as between study comparability for radiographic changes.

Although radiographic changes have been correlated with pulmonary function abnormality in epidemiological studies (7,85), the nature of the relationship between radiographic changes and disability in the individual remains to be elucidated.

1.2.3 Pleural Lesions

Pleural changes are a common consequence of asbestos exposure and take several forms. The four major ones are pleural thickening, pleural effusion, hyaline plaques, and calcified plaques (77, p.189)

1.2.3.1 Benign Pleural Effusion

The exact nature and even existence of this entity is a matter of debate. Preger, in particular, seems skeptical as to the existence of a benign pleural effusion due to asbestos exposure. The diagnosis is in his view "fraught with hazard" (68, p.113) and he feels that at best it may only be made after a long period of follow-up. However, the entity of asbestos-related benign pleural effusion has been accepted by several other authors (8, 21, 27, 77). Pleural effusions may occur along with other symptoms of asbestos related disease including malignancy. In the latter case obviously the diagnosis of benign pleural effusion is not tenable. However, an effusion may be the primary clinical manifestation of asbestos exposure.

1.2.3.1.1 Pathology

The pleural surfaces involved show evidence of an exudative reaction. The fluid is serofibrinous or serohemorrhagic and may include white blood cells; predominantly lymphocytes, and red blood cells. The presence of asbestos bodies in the fluid is rare.

1.2.3.1.2 Clinical and Laboratory Findings

By definition the effusion should resolve without treatment. However, there may be residual pleural thickening and recurrences. The clinical presentation may include acute onset of chest pain and fever with the elevation of the white blood count and erythrocyte sedimentation rate at the one extreme, or it may present with a more indolent onset and chronic accumulation of exudate with minimal symptoms.

1.2.3.2 Pleural Thickening, Plaques, and Calcifications

There seem to be two types of pleural reaction to asbestos exposure. One is a widespread exudative reaction which affects both visceral and parietal pleura. It is usually associated with parenchymal changes and may lead to adhesion formation. The second reaction is a local one, although it may be multi-centric. It consists of plaque formation, usually on the parietal, but occasionally on the visceral pleura. These plaques may hyaline or calcified.

1.2.3.2.1 Gross Pathology

Pleural thickening consists of fibrous tissue which may range from a thin layer to changes several millimeters in thickness. The adhesions which can be formed between the visceral and parietal pleura may be teased apart by manipulation. The plaques themselves appear as raised, whitened areas visible on the pleura and may range up to 50 cm^2 in size (77); hyaline plaques are like cartilage in consistency. Macroscopically, calcified plaques are essentially the same as the hyaline ones with the addition of calcium salts. Naturally, this changes their consistency so that they may be broken and crumble when pulled off the pleura. It is unsure exactly why the calcification occurs, but it is likely that calcified plaques develope by the coalescence of many small centers of calcification in a hyaline plaque (45). Microscopic calcification probably occurs in most asbestos-related chronic pleural changes.

1.2.3.2.2 Microscopic Pathology

Pleural thickening due to asbestos cannot be differentiated from that due to other causes. The process is one of collagen production in the connective tissue underlying the pleura. When the visceral pleura is affected, the fibrotic process may be contiguous with concurrent parenchymal fibrosis.

Pleural plaques are also composed of collagen, arranged in a laminated pattern. The deposition seems to be between the pleura and its overlying mesothelium. Few cells are seen in the region of the plaques, leading to some speculation as to the pathogenetic mechanism. One possibility is that plaques may form from the underlying connective tissue by the action of fibroblasts. Another potential mechanism is that fibrin is deposited on top of the mesothelial layer and is turned into collagen without fibroblasts. A new mesothelial layer then grows over the top of the plaque. Calcified plaques are essentially the same as hyaline plaques with the addition of calcium carbonate and phosphate. Calcification appears to start in the center of the plaque or in the centers of mammilations on the plaque and progressively extends to calcify the entire plaque.

1.2.3.2.3 Clinical and Laboratory Findings

As pleural changes are usually associated with some degree of parenchymal change, precise assessment of their contribution to patients' symptomatology is difficult. Pleural thickening occasionally may be so widespread that it may produce severe dyspnea. Physical findings in these cases may include decreased breath sounds, dullness to percussion, and decreased chest expansion (77). With less marked pleural involvement, pleural changes may not have any symptomatic effect and may be detected on pulmonary function tests only as small reductions

in lung volume (5,52). Pleural changes may be found on chest radiographs before they are detectable by other means.

1.3 Reactions of the Lung to Asbestos Dusts

1.3.1 Respirable Dust

1.3.1.1 Dust Factors

The development of lung disease in response to asbestos exposure must be viewed as the final step in an interaction of a susceptible host to pathogenic particles of asbestos. Whether or not disease will be produced and the nature of this disease depends on a large number of factors starting with dust itself. There has been speculation on which properties of asbestos are responsible for its pathogenic effects and whether different properties are responsible for carcinogenesis and fibrogenesis. Several variables have been suggested as being of importance (17). Among these are the content of silica and other impurities in the asbestos, the size and shape of the particles, the type of asbestos, and the chemical and electrostatic properties of the particles. Some of these issues are of more than theoretical importance as other natural and man-made fibers might also be implicated in human disease based on properties shared with asbestos.

Initial speculation that the silica content was important may have been based on the knowledge of the fibrogenic effects

of silica exposure. However, while exposure to both asbestos and silica was often found in the same worker, it became evident that exposure to asbestos alone was capable of producing pathologic changes. This led to an interest in the size of the particles themselves and the hypothesis that only certain sizes of particles were harmful. At first it was believed that only long fibers (longer than 20 um) were capable of inducing fibrogenic responses, although later animal studies have shown that fibers less than 5 um long can also produce fibrosis (77). Since then results with short fibers have been mixed. Comparability of different studies has been a problem, and it is probably best to consider the matter of particle size unsettled at present (59,67,81). The matter is of some practical importance in deciding which fibers need to be counted for hygiene standards.

Speculation has also focussed on the pathogenicity of the various types of asbestos (43). Again comparisons across studies are difficult and results are not entirely consistent. There is also the problem that multiple factors may be at work. For example, it may be that chrysotile is a particularly active form (71) but that the human body may also clear it more rapidly (46).

1.3.1.2 Host Factors

Host factors are also likely to be of importance in the development of asbestos induced disease. Thus, no population

studies have have shown a 100% prevalence of asbestos induced changes, no matter how high the exposure. Many suggestions have been made regarding which host characteristics are of importance. Obviously only those particles which are taken into the body and retained for a sufficient period in an active form will be capable of inducing changes. Thus the total dust in the environment may not be representative of the inhalable dust, due to the characteristics of the human upper and lower respiratory tract as a dust sampler (63). Not only may the total count be incorrect, but the mix of particle sizes may be different from that reaching the lung.

Deposition of particles in the lung may also been related to variables that remain constant for a given worker, such as airway anatomy (42) and to variables that would change over time, even for the same person, such as tidal volume, respiratory frequency and possibly residual volume (16). Recent interest has also focussed on immunological differences in people as a basis for differing responses (43,84).

Deposition of particles in the lung occurs principally by sedimentation, inertial precipitation, and diffusion. The other side of the equation is the lung's clearance of the deposited particles. The two main mechanisms by which particles are cleared are the mucociliary transport system and the lung macrophages. One might postulate that there will be individual differences in the efficiency with which these systems work, but the net clearance of particles is more complex. As already mentioned, the type of asbestos dust may

affect the clearance rate. In addition a number of other factors may come into play. These include concurrent illness, such as bronchitis or upper respiratory infection, as well as exposure to other environmental pollutants. Some factors, for example smoking, may have variable effects on clearance and in addition may affect the site of deposition. In smokers particle deposition tends to more central than in non-smokers (51).

1.4 Exposure-Response Considerations

1.4.1 Importance of Exposure-Response Relationship

The demonstration of an exposure-response relationship is of central importance in the attempt to prove a causal link between an environmental agent and a pathologic response, as well as being of importance in setting standards for occupational exposures. The existence of such a relationship has been considered as one of the criteria for assessing whether an association is causal (34,77). It is in recognition of this that several studies have attempted to define a dose-response effect between asbestos exposure and both malignant and non-malignant disease.

Despite the difficulties inherent in any retrospective estimation of exposure, several studies have demonstrated an exposure-response effect in both malignant and non-malignant (4,10,11,33,41,55,56,58,73,78,79,80,86,87) asbestos related disease. Demonstrating an exposure-response relationship is

useful for reasons other than trying to prove causality. It may allow some estimation of risk to workers currently undergoing a similar exposure. Within certain limitations, response to past high exposures may allow extrapolation to current workers who are exposed to only a fraction of past levels. Medico-legally, exposure-reponse relationships may provide some scientific basis for litigants in court. From a scientific point of view, exposure-response relationships may allow one to draw conclusions about the merits of competing theories of pathogenesis. An example of this would be the multi-hit or multi-stage theories of carcinogenesis.

1.4.2 Modeling of Exposure-Response Relationships

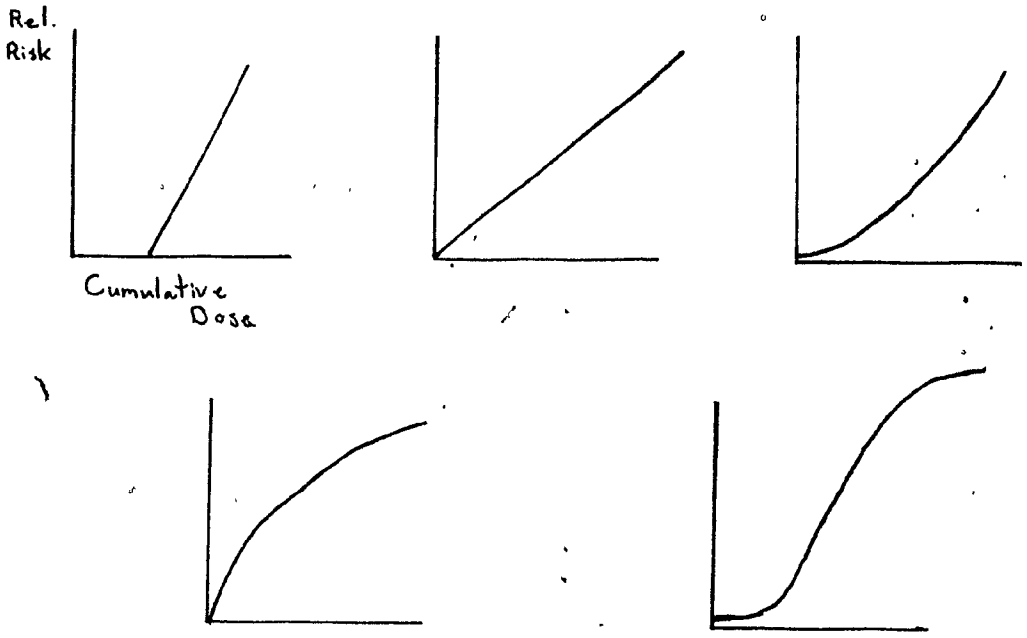
For some of the reasons stated in the preceding section there has been an increased interest in modeling exposure-response relationships. Most of this work has been concerned with malignant rather than non-malignant disease. In principle, modeling should also be possible with non-malignant disease although the shape of the relationship will change with the underlying biology. In addition, it is more difficult to define the onset of a chronic non-malignant process such as fibrosis than it is to define the onset of a malignancy.

The concept of dose-response did not originate with epidemiologic studies but with pharmacology. In pharmacology, the dose administered can be measured with some degree of accuracy. In environmental and occupational studies usually

only crude estimates may be made. To emphasize the difference, the term 'dose-response' may be reserved for pharmacologic and laboratory studies where an agent is actually administered to subjects. The term 'exposure-response' relationship may be used in studies where environmental measurements are made of the amount of a substance to which people have been exposed. Even in pharmacology, where accurate doses can be specified, there is doubt whether a single dose-response relationship may be rigidly defined. Thus one major text includes the caveat, "There is no single characteristic relationship between intensity of drug effect and drug dosage" (25). The authors add the explanation that while ideally the relationship between dose and response would be determined by equilibrium conditions, in reality the curve is derived from peak effects after single doses.

Enterline (23) presents five basic relationships between response and dose. All of these have the same variables on the X and Y axes, that is cumulative dose and relative risk. These are illustrated below (Fig. 1). In addition, Cornfield (15) has proposed a hockey stick model with a low linear slope at low doses and a higher slope at high doses.

Figure 2 Theoretical Dose-response Relationships(78)



One recent article on dose-response modeling (2) makes the point that dose-response relations should be based on a sound theoretical understanding of the underlying biology. At present this is not possible and so models are judged on their empirical fit to data. Although the above article dealt with malignant disease the same is true of non-malignant asbestos induced disease.

A central problem in describing dose-response or exposure-response curves is how to fit the curve at low doses. Often the data at these levels of exposure are not available or are inconsistent (44,76). One is left with extrapolating from high doses or using animal data. Schneiderman (76) points out that it is not possible to get lifetime risks in less than a lifetime. Some biological processes have a maturation time, 50 person-years of observation may be obtained by following 50

persons for 1 year or 1 person for 50 years. By analogy one may argue that 50 dose-years is quite different if it is 50 dose units for 1 year than it is if it is 1 dose unit for 50 years.

1.4.3 Previous Exposure-Response Findings in Non-malignant Asbestos Related Disease

Sheers & Templeton (78) were amongst the first to try to relate fibrotic changes to the severity of asbestos exposure. In their study however, only very crude non-quantitative judgments could be made about workers' total exposure. Their subjects, British naval dockyard workers, were classified as having been continuously, intermittently, or insignificantly exposed, depending on their trade. Data were available on the number of years since first exposure for each man. The prevalence of pleural plaques, extensive pleural thickening, and radiographic signs of pulmonary fibrosis was related to both these exposure variables. A later publication (33) extended the study to three other dockyards with similar results.

Similar problems in specifying exposure were encountered in the study of South African miners by Sluis-Cremer (79). Exposure variables used were length of exposure and length of residence time in the lung. Both these variables were related to the onset of asbestosis. Diagnosis of asbestosis was made on the basis of radiographic findings. A subsequent study in

South African miners (80) found a relationship between years of exposure and the prevalence of thickening of pulmonary interlobar fissures.

The prevalence of cough was found to be related to asbestos exposure in Finnish miners (58). In this study, workers who had been employed for 10 or more years in mines or mills were used as a high exposure sub-group in an attempt to grade exposure.

A study of Australian asbestos cement workers (4) placed men in one of 5 exposure groups based on their job histories. Although the authors probably were able to categorize workers with a reasonable degree of accuracy, no quantitative measures were available. The study found that the per cent predicted 1-second forced expiratory volume (FEV_1) and FVC decreased with severity of asbestos exposure.

Three sets of studies have attempted to quantify asbestos exposure. One set of studies looked at American asbestos cement workers (85-87). Exposure was based on dust counts, in millions of particles per cubic foot (mppcf), taken at various locations in the plant between 1952 and 1969. Estimates on the levels before 1952 were based recollections of long term employees. Annual dust estimates for each work area were prepared and then each worker's job history was examined to derive an estimate of the total dust (in mppcf-years) to which each worker had been exposed. The earliest study showed a clear relationship between total dust exposure and the prevalence and profusion of lung opacities on radiograph (85).

A later study (86) showed the same relationship between dust exposure and maximum mid-expiratory flow (MMF), vital capacity (VC), FVC, and FEV_1. A third study compared the effect of equal (in mppcf-years) exposures of chrysotile and crocidolite (87). Results indicated that crocidolite may have a greater fibrogenic effect on the lungs than chrysotile.

Another group of studies, probably the most extensive yet reported, has been that on Quebec miners and millers (7,9,41,49,55,56,73,77). This group of workers was exposed to chrysotile only, with the exception of one mine where there was a trace of amphibole. Exposures were calculated in a manner similar to the American asbestos cement workers. Dust counts (in mppcf) had been kept since 1948 at various locations. From these measurements, knowledge of environmental conditions, and the recollections of long-term employees, dust values for all jobs during each year of mining operation were calculated. Again complete work histories were available for each worker. Three papers presented the relationship between respiratory symptoms, lung function changes, and radiographic changes with dust exposures (7,55,73). The respiratory symptoms study used each worker's cumulative dust exposure, in mppcf-years, as the exposure variable and and examined the relationship of workers' responses on the Medical Research Council (MRC) respiratory symptoms questionnaire to this measure of exposure. The symptom of breathlessness was the only one that was more closely related to dust than smoking. The lung function study used exactly the same exposure measure and found that several

lung function tests distinguished workers in the lower exposure groups from those in the higher exposure groups. These were inspiratory capacity (IC), FEV_1, and FVC. The tests were more sensitive for smokers than for non-smokers.

The radiographic changes study is of interest in that several exposure variables were used. In addition to the previously mentioned total dust measure, a time weighted dust exposure was calculated, which increased the weighting given to earlier dust exposures. This takes into account their longer residence time in the lung. An effort weighted index was also calculated. This weighted the dust exposure in strenuous jobs differently than the more sedentary exposures to account for different patterns of particle deposition in the lung during exertion. Years since first exposure and total years of exposure were two additional exposure variables used. The study attempted to relate the prevalence of radiographic changes to the exposure variables. A score was calculated for each man's radiograph to take into account the opinion of 6 readers, further details are given in the original paper. Variables that were scored included small rounded opacities (SRO), small irregular opacities (SIO), large opacities (LO), pleural thickening (PT), ill-defined cardiac outline, pleural calcification, costo-phrenic angle obliteration, and ill-defined diaphragm. Workers in two areas, Thetford Mines and Asbestos, were included in the study and separate analyses were carried out for each area. At Thetford, the SRO score was related to total dust and to the effort weighted dust index.

At Asbestos, this score was only related to years of exposure. For SIO, the radiologic change thought to be most characteristic of asbestosis, the score was most closely related to total dust and, to a lesser extent, to years since first exposure at Thetford. At Asbestos, the relation was strongest to years of exposure and to time weighted dust index. Large opacities showed little relation to any measure of exposure in either area. However, the prevalence of ill and well defined large opacities was less than 1%. Pleural thickening was most closely related to years since first exposure and to time weighted dust index in both areas. Ill-defined cardiac outline was related to various measures of exposure, but the pattern varied with age group and no simple explanation could be provided. Pleural calcification was related to time weighted dust exposure only in younger men and to years since first exposure for older men. The simplest explanation seems to be that given a certain minimal dust exposure, pleural calcification is age related. Costo-phrenic angle obliteration was related to age and to total dust exposure at Thetford, but only to age at Asbestos. Ill-defined diaphragm was related to age and to total dust in both areas, but to a greater extent at Thetford than Asbestos.

British asbestos textile workers were the subject of a third set of papers (10-12). One goal of the authors was to examine exposure-response relationships with a view to estimating an acceptable hygiene standard. The methodology for calculating dust exposure was much the same as in the previous

two sets of studies. One significant difference is that fiber counts, rather than particle counts, were used as a measure of dust exposure. Fiber counts were available from 1961 on, but between 1950 and 1961 particle counts were made which had to be converted to fiber counts. Pleural thickening and small opacities on the chest radiograph were related to cumulative dust exposure, as were a decrease in FEV_1 and FVC. In one paper (11) an attempt was made to relate the clinical diagnosis of 'possible asbestosis' to a series of exposure-response curves. These curves assumed various half-lives of dust elimination from the lung, with time-weighted dose (half-life infinity) and cumulative dose (half-life zero) setting the outer limits on the curves. However, the data were not sufficient to pick one model over the others, on the basis of statistical fit. Any model in which the half-life of elimination was greater than three and a half years provided a satisfactory fit to the data.

1.4.4 Defining Exposure

As the above review shows, there are many problems with defining exposure. One of the most formidable is that estimates of dust concentrations have to be made for periods before such measures were carried out. In most cases dust levels were higher 40 or 50 years ago than they were when the first measurements were made in the late 1940's and the 1950's. Two solutions have been used for this problem. One is

to estimate previous exposures on the basis of employee recollection, the other is to multiply more recent measurements by a correction factor. Even for periods for which there are measured dust levels, there remains the problem of relating job dust to an individual. There may be wide variations in the amount of dust that individuals are exposed to while performing the same job. This may be especially true in jobs where dust levels are to some extent determined by individual work habits. A third problem concerns changing units of measurement over time. Earlier dust counts are in particles per cubic foot, more recent ones are usually in fibers per cubic centimeter. One measure may be converted to the other as was done by Berry et al (10), but others state that there is no consistent relationship between the two units that permits this (56). Current hygiene standards are in fibers per cubic centimeter. Beyond the issue of measurement units is the problem of relating environmental exposure to the dose that a worker actually ingests or inhales. There is no easy solution to this and some of the difficulties are detailed by Vincent & Mark (82).

With all these difficulties in estimating an individual's exposure, it is almost inevitable that there will be appreciable errors in assessing worker exposure. These errors may tend to work in one direction and bias dust estimates as Berry et al (10) admit with their probable underestimation of early dust concentrations. However, even random error may have unfortunate results when exposure-response curves are fitted to

data. Thus, even if the error in measurement is unbiased, it may lead to a biased estimate of the exposure-response relationship by flattening the exposure-response relationship, overstating the health risks at low exposures, and understating the rate of increase with exposure (3,11) or changing the shape of the relationship (66).

Apart from measurement considerations, there is the problem of which particles and/or fibers are of importance. In general it is believed that account should be taken of particles of respirable size for fibrotic lesions, and perhaps of larger than respirable size for bronchitic lesions (59). Perhaps some should be weighted more than others. These issues are likely to remain unsettled for some time to come.

There are many ways to calculate exposure, as demonstrated by the previously cited studies. The simplest form, cumulative exposure, provides a measure from which one may derive an exposure-response relationship. From a biological point of view it is not a satisfactory measure as it does not account for the fact that changes may appear and progress years after exposure has ended. The time weighted index is more satisfactory, but it does not take into account the postulated elimination of dust from the lungs. However, not all particles of inhaled asbestos may be harmful to the same degree, and different classes of particles may be eliminated at different rates. Furthermore, it is not known whether the minimum retention time for dust to evoke a response is days, months, or years. This would have to be known if a time-weighted index

was to be derived from anything other than empirical grounds. In addition there are a number of other exposure variables which might be related to subsequent response. Clearly the theoretical understanding of the underlying biology is not sufficient to allow any firm conclusions on exactly what aspects of exposure are the most significant.

1.4.5 Defining Response

If it is assumed that radiographic and pulmonary function test changes are true reflections of the underlying pathology that one is attempting to measure, then perhaps response is more easily defined than exposure. Practical problems in defining response may still occur. The changes that are measured may well be due to factors other than asbestos, working either separately or in conjunction. Examples of this include smoking, aging, and infection. Another practical problem may be that the prevalence or score of what is measured may not yield enough responders, or a wide enough range of response, to define reliable exposure-response relationships. Previous studies have tended to group responses by the nature of the response measure used, that is pulmonary function test changes, or x-ray changes, or questionnaire responses. This may have lent a certain artificiality to the responses. Not all x-ray or pulmonary function test changes are indicative of the same underlying pathology. If one is attempting to measure a certain type of biological response, a combination of these measures may be more appropriate than each in isolation.

1.5 Summary

There remains little doubt that asbestos exposure is associated with a host of non-malignant effects on the respiratory system. Exposure-response relationships have been convincingly demonstrated in several independent studies. In general, data have not been sufficient to delineate a single exposure-response relationship but rather, have been compatible with a range of such relationships. Past studies have been bedeviled by problems of operationalizing exposure and response.

As already mentioned, dust or fiber measurements in the air are only an approximation of what is delivered and retained in the lung. Even if accurate measurements of the asbestos dose retained by the lung were possible, it is conceivable that measures other than the simple summation of annual dust exposures would show a stronger relation to response. In other words the profile of exposure may be important.

If this is correct, the selection and incorporation of dust variables other than the sum of annual dust exposures may improve the exposure-response relationship. There are several different non-malignant responses to inhaled asbestos, which may be related to different aspects of exposure profile. The elucidation of aspects of exposure profile that are related to subsequent response may be of importance in setting exposure limits to asbestos in the present or future.

2 STUDY OBJECTIVES

The goal of this study was to determine if certain facets of human exposure to asbestos, in addition to that described by cumulative dust exposure, are related to subsequent non-malignant respiratory tract abnormalities. It was expected that exposure-response relationships could be more clearly defined through the identification of such features, and their incorporation into the description of exposure.

Intermediate goals were the development of additional exposure variables, to describe profile of exposure, and the development of suitable response measures.

It was proposed that these goals be attained through the use of existing data on a previously defined subset of Quebec asbestos miners and millers.

It was anticipated that the results of the study might serve two purposes. First, the identification of facets of exposure that lead to subsequent morbidity might have implications for hygiene standards at present and in the future. A second potential benefit from the study results was to increase understanding of the pathogenesis of the respiratory tract changes under investigation:

2.1 Definitions

Facets of asbestos exposure - This refers to variables which would characterize an individual's profile (temporal

pattern) of exposure to asbestos while working. These variables could have dimensions of time, dust/volume or a combination of the two. A complete listing of these variables is found in Table 7 in the next section.

Cumulative dust exposure - This is also referred to as total dust. It is calculated by summing the annual estimates of an individual's dust exposure over his working years.

Existing data - This study would use data already collected in conjunction with a previous study (7,55), but analysis would be performed with a view to answering different questions than had been addressed previously.

Non-malignant respiratory abnormality - This will encompass abnormalities reflected by the development of respiratory symptoms, changes on chest x-ray, and pulmonary function changes.

2.2 Design

The study was carried out in three steps. The first entailed the selection and combination of response measures into response scales. Factor analysis was used as a tool to aid in the derivation of clinically comprehensible scales.

The second step consisted of the construction of variables that described the various facets of an individual's profile of asbestos exposure. As the study was exploratory rather than hypothesis testing in its objectives, these variables were not constructed with a particular theory in mind. Of course

previous studies suggested certain aspects of exposure that should be included in these variables.

The final step in the study made use of regression analysis to determine which facets of exposure are related to the previously constructed response scales once cumulative exposure (total dust) has been taken into account. Appropriate safeguards were taken to control for the effects of other variables that may influence respiratory status, such as age and smoking.

3 METHODS

3.1 Description of the Existing Data Set

3.1.1 Description of Study Subjects

The data used for this study were collected in the late 1960's and a number of findings have already been published (6,7,9,47-49,55,56). The group of men whose health and exposure status formed the basis of the present study was essentially the same as that reported on in the 3 studies cited above. The men were an age stratified sample of the 6,180 men who were working for Quebec asbestos mining companies in the Thetford Mines and Asbestos areas on October 31, 1966. The sample excluded all those younger than 21 and all those older than 65. The remainder were placed in quinennial age groups and a sample was drawn from these groups in the ratio given below.

Table 4 Weight of Sample by Age Group

Age Group	Weight in Sample
21-25	4
26-30	5
31-35	6
36-40	7
41-45	8
46-50	9
51-55	10
56-60	11
60-65	12

The sampling ratio was somewhat arbitrary but was necessary to ensure that enough men with high exposures would be included in the sample. Samples for each age group were drawn from all eight mining companies in proportion to the total number of male employees each company had at that time. This procedure should have yielded a sample of 1,080 men but as there were not enough older employees in some of the companies, the actual sample comprised 1,027 men. By the time that testing was carried out in 1967, 85 men had died or were not available, and 57 refused to participate. This left 885 men who were examined. To increase the number of older workers in the study all remaining men in the oldest age groups were included in a second field study in 1968. Of the 241 men eligible, 184 were examined. This yielded a total sample of 1,069. Deficient data on 81 men necessitated their exclusion from analysis, leaving 988 men on whom there were sufficient data for the purposes of the present study.

3.1.1.1 Data Available

Data available on each man consisted of descriptive information as well as estimates of dust exposure and response to dust exposure as outlined in the following sections. Each man's birth date was available as was the date on which his pulmonary function tests were carried out and the date he started working. Heights and weights on the test date were also obtained on each man. An estimate of cigarette intake per

day was available for smokers. Each man was coded as of the test date as a non, current, or very rare, or ex-smoker.

3.1.1.2 Verification of Data

Although the data were on computer tape and had already been checked before use for previous studies, an attempt was made to ensure that the data were as free from errors as possible. To this end, frequency distributions were obtained for several variables and men with out of range data were deleted from further analysis. In one case, this involved a man's age and in others questionaire items. Five men were dropped for this reason, all further analyses were performed on the remaining 983 men. In addition to checking for out of range data, total dust exposures were calculated using the annual dust exposures for each man and compared with the total dust coded on the tape. In all cases, the calculated total dust was identical with the coded total dust.

3.1.2 Dust Data

Dust measurements had been carried out at all eight companies starting in 1948. These measurements were carried out almost annually until 1966 at various sites around the mining and milling operations by the same observer using a midget impinger. Measurements were made in millions of particles per cubic foot. Over 4,000 separate counts were made

during the 18 year period. Estimates of dust conditions before this time were based on recollections of long time employees. A dust exposure for workers performing each job at a mine or mill was calculated, based on the dust readings at various sites and the knowledge of where workers performing each job were located. As dust conditions had changed over time, the dust exposure in each job was calculated on an annual basis from 1904 to 1966. As the number of hours in the work week also had changed over the years, appropriate corrections were made to account for this. An annual exposure could be obtained for each worker by checking his employment history to find out which jobs he performed in which years and then matching this with the dust levels prevailing in that job during a particular year. A worker's cumulative exposure was the sum of his annual dust exposures. Work histories were maintained to the nearest month.

Further details on dust conditions and the calculation of workers' exposures may be found in a paper by Gibbs & Lachance (28).

3.1.3 Pulmonary Function Tests

Pulmonary function tests were carried out during 1967 and 68 on all men in this study. Procedures and full information on the measurements taken are given in detail elsewhere (6). For the purposes of this study, 3 basic measures of respiratory function were used. They were FVC, FEV_1, and MMF. To allow

comparison between men of different ages and heights, a predicted FVC, FEV_1, and MMF were calculated for each man using previously developed regression equations (30). Different equations were used depending on each man's smoking status. The final variables used as indicators of pulmonary function were the per cent predicted FVC, FEV_1, and MMF. For example, per cent predicted FVC for each man was his measured FVC divided by the FVC predicted on the basis of his age, height, and smoking status, multiplied by 100.

3.1.4 Respiratory Symptoms

At the same time that pulmonary function testing was carried out, men were questioned regarding any respiratory symptoms they might have. A slightly modified form of the British Medical Research Council questionnaire on respiratory symptoms (1966) was used. Questionnaires were available in English or French, depending on the individual's preference. An English version of the questions is found in Appendix 1. Questionnaires were administered by a fluently bilingual interviewer. Though it was thought unlikely that all symptoms recorded would be related to asbestos exposure, it was nevertheless decided to use them all in the preliminary analyses to set up response scales.

3.1.5 Radiographic Data

Annual chest radiographs had been taken of all employees since 1948. The most recent chest radiograph of each man in the study was read independently by 6 readers using the UICC/Cincinnati classification. Only some of the abnormalities coded were used in this study. These were the small irregular opacities (SIO), small rounded opacities (SRO), pleural plaques (PP), and pleural thickening (PT). PT and PP were graded 0,1,2. The SIO and SRO were coded on a 12 point scale; 0/-, 0/0, 0/1, 1/0, 1/1, 1/2, 2/1, 2/2, 2/3, 3/2, 3/3, 3/4. To arrive at a single score on these 2 variables it was decided to take the average of the scores given by the 6 readers. To facilitate this the scale was recoded as 1 to 12.

Radiographic data on each man thus consisted of 4 scores. These were the scores for SIO, SRO, PT, and PP on his most recent chest radiograph, averaged across the 6 readers.

3.1.6 Advantages and Disadvantages of Study Data

There are both advantages and disadvantages inherent in the use of existing data. These data were originally collected for a series of studies already published. Records on men's employment had been kept by companies since the industry's inception in the last century. Records were kept for payroll and production purposes, not epidemiological ones. Hence, the job classification scheme adopted by eight different companies

had to be adopted, as is. The passage of time made it difficult to verify the accuracy of all records and the possibility of inconsistencies in record keeping over time cannot be ruled out. Certain aspects of company records could be checked, for example, employee ages. Upon checking it was found that in some cases errors had been made in company records.

Problems with existing dust data are even greater. Although there were thousands of readings taken after 1948, there were many work areas for which information was missing. Even had dust information been available for all sites, the use of site dust levels to calculate a dust exposure for each job involves many assumptions, not all of which may hold true. The units of measurement are another problem. Measurements of dust were made using midget impinger and were given in mppcf and not in fibers/cc as is the current practice. There is no reliable conversion factor between the two units. The estimation of dust levels before 1948 introduces an unknown, but potentially substantial, amount of error into any measure of exposure. Early dust counts were based on techniques with lower sensitivity than those after 1960; this introduces a possible source of bias in studying time relationships with these data.

Measurements of response were collected by investigators in the 1960's under more rigourous conditions than were the dust levels. The pulmonary function and questionnaire data are as good as can be reasonably expected. The chest radiographs were all taken around the time of the study, and while of

varying quality, were probably adequate for the purposes of the study. They were, as already stated, all interpreted by the same readers under conditions designed to maximize consistency.

The criterion for selection of the men in the study also poses some difficulty. They are survivors of their particular birth cohort. The degree of selection bias is probably age dependent. It seems reasonable to assume that the men in the older age groups will be more highly selected than those in the younger ones. A greater percentage of the men in these age groups will have died or retired. The cause of death or reason for retirement may have been occupationally related. The relationship between exposure and response may have been different for these men than for those remaining in the work force.

While there are many difficulties with the data they also provide an unusual opportunity to study the effects of patterns of asbestos exposure in humans that may not readily occur again. Thus the usual advantages of using existing data, saving time and money, are overshadowed by the unique opportunity that these data present. Current hygiene standards permit exposures to only a small fraction of the asbestos to which men in this study were exposed. It is unlikely that group of men with such exposures could ever be assembled again. It is this, more than anything else that outweighs all the weaknesses with the data. These data may be imperfect but they appear to be the best available to answer questions about

the effect of exposure profile on subsequent respiratory tract changes.

3.2 Development of Variables

3.2.1 Exposure Variables

Exposure variables were generated without any particular hypotheses in mind, but were constructed on the basis of what previous investigators had found and on what seemed biologically plausible.

Total dust had been found to be related to response measures in other studies and so was included as the primary exposure measure in this study. Because the relationship between total dust and response may not be linear, a higher order term, $(\text{total dust})^2$, was included. There has been speculation that residence time of dust in the lung may have a role in the development of subsequent disease. To check for this possibility a variable that weighted each annual dust by the number of years it had been in the lung at the end of the study was included. Other variables included one that weighted each dust by the worker's age during that year and a related variable that weighted each dust by the number of years since the man had started working. Another variable weighted each dust according to the calendar year in which it had occurred. One variable consisted of the sum of the $(\text{annual dusts})^2$, a subtle difference from $(\text{total dust})^2$. The reason for calculating both these variables was that men who had a few

years with very high exposures will have have a higher score when their (annual dusts)^2 are summed than men who had the same total dust (and therefore total dust^2) made up of a steady series of annual dusts. Simpler variables included time since first exposure, net years of exposure, peak dust, average exposure, number of years with dust greater than 5 mppcf, and dust exposure in the first 5 years on the job. A complete list of these variables is given in Table 7.

It was not expected that the same exposure variables would be of importance in different types of response. The goal in defining the exposure variables was to come up with a managable number of easily calculable variables that would allow a variety of exposure profiles to be described.

3.2.2 Response Variables

Response variables available have already been described. For the purposes of this study it was decided that sets of variables that might indicate the same underlying biological response would be grouped together into response scales. The scales would be linear combinations of the response variables. These response scales would then constitute the dependent variables in a series of multiple regressions against the exposure variables in the final stage of the analysis.

3.2.2.1 Selection of Response Scales

Two considerations were of prime importance when constructing the response scales. First, it was felt that the different scales should be clinically coherent and second that they should be constructed so that variability in the data was taken into account. Factor analysis was used in attaining this goal. It should be emphasized that the factor analyses were exploratory, not hypothesis testing, and were all performed without reference to the exposure variables.

In the first place, it was decided that at least two response scales should be derived from the data. This was because at least two types of clinically recognizable responses were expected, possibly centering on the parenchyma and the airways. For practical reasons a maximum number of factors was also specified. For the first analysis this was set at 6. The first factor analysis was performed on the 4 radiological variables (SIO, SRO, PT, PP), the 3 pulmonary function variables (FVC, FEV_1, MMF), and the respiratory symptoms questions. The 6 factors that emerged from this analysis could best be described as cough, sputum production, catarrh, chest illness, pulmonary function changes, and breathlessness. These 6 factors could not readily be understood in clinical terms and there was no factor on which radiographic changes loaded heavily.

A second attempt was made using 3 separate factor analyses. For these analyses it was decided to group

measurements that might be expected to reflect the same clinical changes. These were: i) mucous hypersecretion reflected in questions 52-67, ii) airflow limitation reflected in the pulmonary function tests and the symptom of breathlessness, and iii) pulmonary fibrosis reflected by radiographic changes and the symptom of breathlessness. In this analysis, 2 factors were requested. This resulted in one factor where no one question had a very heavy weight, although questions 52-57 were weighted the heaviest. Only question 66 had appreciable weight on factor 2. In the second analysis, only one factor was asked for and only FEV_1 had a high weighting on this factor. In the third analysis, SIO had the highest coefficient, all other variables had coefficients in the 0.11-0.17 range.

Based on the results of this analysis, it was decided that one of the response scales would consist of FEV_1 alone. Further definition of the other scales including the x-ray changes and respiratory symptoms was required.

To this end, the respiratory symptom questions were re-analyzed omiting questions 64-66. These were questions regarding nasal catarrh, a symptom which was felt to be irrelevant to pathological lung changes. An analysis asking for 2 factors without the inclusion of catarrh seemed to indicate 3 subsets of respiratory symptoms: i) cough (questions 52-54), ii) sputum production (questions 55-57), and iii) other symptoms related to airway responsiveness (questions 58-63,67).

It was felt that cough and sputum were manifestations of

the same underlying changes. Breathlessness and questions 61-63 and 67 were felt to be separate. The respiratory symptoms questions were again re-analyzed; the cough and sputum questions were analyzed separately from questions 60-63 and 67. The new cough-sputum factor gave almost identical weights to cough and to sputum. The relative weights of the three cough questions were almost the same as the corresponding sputum questions. The question, "Do you cough (bring up phlegm) like this for more than 3 months out of 12", was given the heaviest weight. The other questions, 60-63 & 67, were analyzed separately and all had coefficients greater than 0.11.

The radiographic variables and the breathlessness question, 60, were re-analyzed using 2 factors. This analysis seemed to indicate that there were 2 groupings of variables consisting of SIO, SRO, and question 60; and another grouping consisting of PP and PT. These 2 groups were analyzed again separately to further refine the relative weightings. FVC was added to SIO, SRO, and question 60 because it was a clinical concomitant of the other variables.

The 5 response scales derived by the preceding analysis were:

1) -100FEV

2) 4SIO + SRO + 3Q60 - 3FVC

3) PP + PT

4) -(2Q52 + Q53 + 3Q54 + Q55 + Q56 + 4Q57)

5) 4Q60 + 3Q61 + Q62 + 2Q63

Clinically, they can be conceptualized as:

1) airflow limitation

2) pulmonary fibrosis

3) pleural fibrosis

4) mucous hypersecretion

5) airway reactivity

Some of the variables were coded negative so that a higher value in any equation indicates greater abnormality.

3.2.2.2 Resp 1 - Airflow Limitation

This is a straight-forward response scale, and the only one that consists of just one of the original response variables. Clinically it is best understood as a response of airflow limitation, and it is not entirely unreasonable that FEV_1 stands alone as such. In order to make the direction of this scale the same as the others the sign was changed from positive to negative.

3.2.2.3 Resp 2 - Pulmonary Fibrosis

This scale includes both the rounded and irregular opacities, as well as one lung function measure, proportion predicted FVC, and one respiratory symptom, breathlessness. The sign for the pulmonary function test is again negative, for the same reason as stated in the preceding section. The respiratory symptom in this scale is that of breathlessness.

Considering all the components on the scale together, the best clinical description of the scale is pulmonary fibrosis.

3.2.2.4 Resp 3 - Pleural Disease

The 2 pleural changes on x-ray stand together as indicators of pleural disease. Their grouping was suggested by factor analysis and again is reasonable on clinical grounds.

3.2.2.5 Resp 4 - Bronchitis

This scale is composed entirely of respiratory symptoms relating to cough and sputum production. These are classically associated with bronchitis. All items on this scale have negative signs because of the way responses were coded. The direction of the scale is consistent with the others, a higher score indicates more extensive symptoms.

3.2.2.6 Resp 5 - Airways Reactivity

This scale is also composed entirely of respiratory symptoms. In addition to the breathlessness question also used on the second scale, it included responses to questions regarding wheezing, shortness of breath with wheezing, and the effect of weather on chest symptoms. These symptoms are most in keeping with reversible airways disease.

3.3 Correlation of Scales

Although the 5 response scales were each supposed to measure different types of response to dust, it seemed reasonable to expect that they would be correlated to some extent, or at least that they would not be negatively correlated. If negative correlations were found one might suspect that the scale was not measuring what it was assumed to measure, or that computational errors had been made. As a further check the correlations of the 5 response scales with total dust and with smoking were obtained. Previous studies had shown that response was related to total dust and some of the response scales, especially bronchitis, could be expected to correlate with smoking. Any unexpected or unreasonable values in the table of correlations might high light potential problems in further analysis. Correlations were calculated using SPSS and are presented below. None of the correlations are unreasonable or inexplicable on the basis of past work.

Table 5 Response Scale, Total Dust, & Smoking Correlations

	Resp1	Resp2	Resp3	Resp4	Resp5	T.Dust	Smoke
Resp 1	1.000	0.344	0.144	0.148	0.310	0.225	-0.117
Resp 2		1.000	0.192	0.254	0.702	0.259	0.090
Resp 3			1.000	0.049	0.076	0.101	-0.001
Resp 4				1.000	0.379	0.119	0.226
Resp 5					1.000	0.204	0.170
T.Dust						1.000	0.073
Smoke							1.000

3.4 Regression Analysis

3.4.1 Computer Program Used

All regressions were performed using the Statistical Package for Social Sciences (SPSS) 'New Regression' program. This allows one a large amount of flexibility in specifying exactly how the regressions are run. It is possible to force some variables into the regression equation and then to add others in a stepwise manner. This was the method used in this study. The p value to enter stepwise variables may be specified by the user, in this case it was 0.3. This level was picked so that any variable that might be at all important in explaining response would be allowed into the regression equation.

Separate regressions were performed for each one of the 5 response scales.

3.4.2 Independent Variables in the Regressions

The objectives for this study were to determine if other facets of exposure in addition to total dust were of significance in predicting response. To take this into account, some variables were 'forced in' to the equation initially. This was to control for the confounding effect of these variables. Once these variables were entered, the remaining exposure variables were entered stepwise by the

regression program if they met the required p=0.3 for entry to the equation. The 2 groups of variables are described in the following 2 sections.

3.4.2.1 Variables Entered Initially

The variables in the following Table were entered initially as a group to the regression equation and were not deleted on subsequent steps.

Table 6 Initial Regression Variables

1) Total Dust
2) Total Dust^2
3) Smoke
4) Smoke^2
5) Age
6) Age^2
7) Smoke X Age
8) Smoke X Total Dust

Total dust was included in this group so that other exposure variables that proved to be significant in later steps would be contributing on the basis of their describing profile of exposure and not because they were contributing a 'total dust' effect. The total dust squared term was added in case there was a non-linear component to the total dust effect. Smoke was included so that differences in exposure profile between smokers and non-smokers would not lead to spurious variables being added later in the stepwise section of the analysis. The smoke dust interaction term was added to check

the possibility that total dust exposure would act differently for smokers and non-smokers. Age and age^2 were included to prevent exposure variables from describing an age effect rather than exposure profile, the smoke age term was included to check for this interaction.

3.4.2.2 Variables Entered Stepwise

Most of variables eligible for entry in a stepwise fashion have already been described. A complete listing is given Table 7 below.

Table 7 Variables Eligible for Stepwise Entry

D2	Dust weighted by age
D3	Dust weighted by residence time
D4	Sum of annual dusts^2
D5	Dust weighted by years since starting job
D6	Dust weighted by calendar year in which it occurred
D8	Number of years with dust over 5 mppcf
D9	Dust exposure in the first 5 years on the job
Peak	Highest annual dust level while working
Avdust	Average annual dust while working
Tserv	Total years working
Fexp	Years since first exposed
Age^3	

All the above were potential descriptors of exposure profile except age^3. It was included in case age had been undercorrected for by age and age^2. This was felt to be unlikely and the inclusion of age^3 was not vital to the purposes of this study.

A number of different dust effects could be expressed through various combinations of the descriptors of the dust profile listed in Table 7. The variables were constructed with several potential effects in mind, the general rationale was to provide variables that would cover as many aspects of exposure profile as possible while keeping calculation and the number of variables to manageable proportions.

4 RESULTS

4.1 Further Characteristics of Study Subjects

Men were selected for inclusion in the study by criteria already mentioned. However, there are a few characteristics of interest that were not part of the inclusion criteria. The most obvious of these is smoking status. The tables below provide further information regarding the men's years since first exposure, their total years of exposure, and their smoking status on the test date.

Table 8 Years Since First Exposure

Years	N	%	Years	N	%
0-5	127	(12.9)	31-35	44	(4.5)
6-10	107	(10.9)	36-40	121	(12.3)
11-15	83	(8.4)	41-45	65	(6.6)
16-20	165	(16.8)	46-50	37	(3.8)
21-25	134	(13.6)	51+	2	(0.2)
26-30	98	(10.0)			

Table 9 Total Years Of Service

Years	N	%	Years	N	%
0-6	146	(14.9)	26-30	100	(10.2)
6-10	95	(9.7)	31-35	90	(9.2)
11-15	99	(10.0)	36-40	68	(6.9)
16-20	162	(16.5)	40+	63	(6.4)
21-25	162	(16.5)			

Table 10 Smoking Status

	N	%
Non-smoker	115	(11.7)
Ex-smoker	130	(13.2)
Smoker	738	(75.1)
	983	(100.0)

The above tables show that the overwhelming majority of men were smokers. The shapes of the frequency distributions for total years of service and years since first exposure are quite similar. This is to be expected since most men were employed fairly steadily in the area. As the variables, years since first exposure and total years of service, are so closely related it is unlikely that there will be much difference in their relationship to the dust variables. Tables 8 and 9 demonstrate however that there is a high degree of variability in the time spent working.

4.1.1. Cross-Tabulations Of Subjects by Age & Smoking Status With Selected Exposure And Response Variables

To provide further information on the relationship of exposure and response to different age groups of workers, the following tables have been prepared (Tables 11-15).

4.2. Dust Variables

4.2.1. Correlation Between Dust Variables

The major component of most of the dust variables was a combination of a man's annual dust exposures, although some of the variables were based only on exposure time. There would be little point in attempting to improve on the response prediction made by total dust if all the other exposure variables correlated nearly perfectly with total dust. To check the degree of correlation between dust variables Table 16 was created.

The correlations in Table 16 range from 0.264 to 0.984, with most tending towards the high end of the range. As could be expected, all correlations are positive. There are some patterns that emerge from Table 16 which are readily explained by the origin of the variables. For example, the two variables containing a squared dust term are more highly correlated with each other than with those containing a linear dust term.

Table 11 Breathlessness by Age and Smoking Status

Age		Severity of Breathlessness 0	1	2	3
21-25	NS	6(75.0)	2(25.0)		
	X	5(100)			
	S	13(72.2)	2(11.1)	3(16.7)	
26-30	NS	7(77.8)	2(22.2)		
	X	3(75.0)	1(25.0)		
	S	28(59.6)	13(27.7)	5(10.6)	1(2.1)
31-35	NS	6(75.0)	2(25.0)		
	X	5(100)			
	S	33(63.5)	13(25.0)	6(11.5)	
36-40	NS	12(70.6)	4(23.5)	1(3.7)	
	X	7(53.8)	4(30.8)	2(15.4)	
	S	43(59.7)	23(31.9)	5(6.9)	1(1.4)
41-45	NS	4(44.4)	4(44.4)	1(11.1)	
	X	11(78.6)		3(21.4)	
	S	37(45.7)	33(40.7)	9(11.1)	2(2.5)
46-50	NS	7(58.3)	3(25.0)	2(16.7)	
	X	5(41.7)	6(50.0)		1(8.3)
	S	46(44.7)	32(31.1)	18(17.5)	7(6.8)
51-55	NS	7(58.3)	3(25.0)	2(16.7)	
	X	8(44.4)	4(22.2)	5(27.8)	1(5.6)
	S	35(39.3)	38(42.7)	10(11.2)	6(6.7)
56-60	NS	9(64.3)	4(28.6)	1(7.1)	
	X	5(33.3)	7(46.7)	2(13.3)	1(6.7)
	S	26(27.1)	40(41.7)	22(22.9)	8(8.3)
61-65	NS	10(38.5)	7(26.9)	8(30.7)	1(3.8)
	X	16(36.4)	17(38.6)	8(18.2)	3(6.8)
	S	49(27.2)	76(42.2)	36(20.0)	19(10.6)

N.B. In Tables 11-15: NS- non-smoker, X- ex-smoker, S-smoker. Numbers are counts in each category with row percentage in brackets.

Table 12 X-ray Abnormalities by Age and Smoking Status

Age		Number of Abnormalities	
		0	1+
21-25	NS	5(62.5)	3(37.5)
	X	4(80.0)	1(20.0)
	S	17(94.4)	1(5.6)
26-30	NS	7(77.8)	2(22.2)
	X	4(100)	
	S	32(68.1)	15(31.9)
31-35	NS	6(75.0)	2(25.0)
	X	1(20.0)	4(80.0)
	S	36(69.2)	16(30.8)
36-40	NS	11(64.7)	6(35.3)
	X	7(53.8)	6(46.2)
	S	42(58.3)	30(41.7)
41-45	NS	7(77.8)	2(22.2)
	X	3(21.4)	11(78.6)
	S	31(38.3)	50(61.7)
46-50	NS	1(8.3)	11(91.7)
	X	6(50.0)	6(50.0)
	S	34(33.0)	69(67.0)
51-55	NS	8(66.7)	4(33.3)
	X	7(38.9)	11(61.1)
	S	29(32.6)	60(67.4)
56-60	NS	2(14.3)	12(85.7)
	X	4(26.7)	11(73.3)
	S	28(29.2)	60(67.4)
61-65	NS	1(4.8)	20(95.2)
	X	8(18.2)	36(81.8)
	S	39(21.7)	141(78.3)

Table 13 % Predicted FEV_1 by Age and Smoking Status

Age		% Predicted FEV_1					
		0-60	61-70	71-80	81-90	91-100	100+
21-25	NS		1(12.5)		2(25.0)	3(37.5)	2(25.0)
	X					4(80.0)	1(20.0)
	S				5(27.8)	7(38.9)	6(33.3)
26-30	NS			1(11.1)	3(33.3)	2(22.2)	3(33.3)
	X					3(75.0)	1(25.0)
	S			2(4.3)	11(23.4)	15(31.9)	19(40.4)
31-35	NS		1(12.5)	2(25.0)	2(25.0)	2(25.0)	1(12.5)
	X			2(40.0)	1(20.0)	2(40.0)	
	S		2(3.8)	4(7.7)	5(9.6)	22(42.3)	19(36.5)
36-40	NS			2(11.8)	5(29.4)	8(47.1)	2(11.8)
	X			1(7.7)	4(30.8)	5(38.5)	3(23.1)
	S		3(4.2)	7(9.7)	13(18.1)	20(27.8)	29(40.3)
41-45	NS		1(11.1)		2(22.2)	5(55.6)	1(11.1)
	X	1(7.1)		3(21.4)	3(21.4)	5(35.7)	2(14.3)
	S	2(2.5)	1(1.2)	4(4.9)	15(18.5)	26(32.1)	33(40.7)
46-50	NS	1(8.3)	1(8.3)	1(8.3)	2(16.7)	6(50.0)	1(8.3)
	X		1(8.3)	3(25.0)	3(25.0)	3(25.0)	2(16.7)
	S	4(3.9)	2(1.9)	17(16.5)	29(28.2)	25(24.3)	26(25.2)
51-55	NS	1(8.3)		1(8.3)	5(41.7)	3(25.0)	2(16.7)
	X	4(20.0)		2(10.0)	5(25.0)	4(20.0)	5(20.0)
	S	4(4.5)	8(9.0)	12(13.5)	19(21.3)	23(25.8)	23(25.8)
56-60	NS		1(7.1)	2(14.3)	4(28.6)	4(28.6)	3(21.4)
	X	2(13.3)	2(13.3)	5(33.3)	3(20.0)	2(13.3)	1(6.7)
	S	4(4.2)	7(7.3)	10(10.4)	27(28.1)	23(24.0)	25(26.0)
61-65	NS	2(7.6)	3(11.5)	5(19.2)	9(34.6)	3(11.5)	4(15.4)
	X	7(15.9)	4(9.1)	9(20.5)	11(25.0)	10(22.7)	3(6.8)
	S	11(6.1)	12(6.7)	37(20.6)	29(16.1)	38(21.1)	53(29.4)

Table 14 Cumulative Dust Exposure by Age and Smoking Status

Age		Cumulative Dust Exposure (in mppcf-y)					
		0-50	50-99	100-199	200-399	400-799	800+
21-25	NS	8(100)					
	X	5(100)					
	S	18(100)					
26-30	NS	8(88.8)	1(11.1)				
	X	4(100)					
	S	45(95.7)	2(4.3)				
31-35	NS	6(75.0)	1(12.5)	1(12.5)			
	X	3(66.0)	1(20.0)	1(20.0)			
	S	41(78.8)	10(19.2)		1(1.9)		
36-40	NS	11(64.7)	4(23.5)		2(11.8)		
	X	4(30.8)	3(23.1)	5(38.5)	1(7.7)		
	S	36(50.0)	11(15.3)	6(8.3)	10(13.9)	7(9.7)	2(2.8)
41-45	NS	5(55.6)	2(22.2)			2(22.2)	
	X	6(42.9)		4(28.6)	2(14.3)	1(7.1)	1(7.1)
	S	30(37.0)	14(17.3)	23(28.4)	12(14.8)	1(1.2)	1(1.2)
46-50	NS	4(33.3)	3(25.0)	2(16.7)	1(8.3)	2(16.7)	
	X	3(25.0)	3(25.0)	3(25.0)	3(25.0)		
	S	38(36.9)	19(18.6)	18(17.5)	10(9.7)	10(9.7)	8(7.8)
51-55	NS	6(50.0)	1(8.3)	3(25.0)	1(8.3)	1(8.3)	
	X	2(11.1)	3(16.7)	2(11.1)	3(16.7)	5(27.8)	3(16.7)
	S	25(28.1)	12(13.5)	20(22.5)	13(14.6)	9(16.7)	10(10.1)
56-60	NS	4(28.5)	3(21.4)	3(21.4)	1(7.1)	2(14.3)	1(7.1)
	X	6(40.0)	1(6.7)	2(13.3)	2(13.3)		4(26.7)
	S	25(26.0)	8(8.3)	18(18.8)	20(20.8)	16(16.7)	9(9.4)
61-65	NS	6(23.1)	2(7.7)	3(11.5)	8(30.8)	3(11.5)	4(15.4)
	X	10(22.7)	5(11.4)	8(18.2)	11(25.0)	6(13.6)	4(9.1)
	S	18(10.0)	21(11.7)	27(15.0)	36(20.0)	40(22.2)	38(21.1)

Table15 Years of Service by Age and Smoking Status

Age		Years of Service				
		0-5	6-10	11-20	21-30	31+
21-25	NS	8(100)				
	X	5(100)				
	S	16(88.9)	2(11.1)			
26-30	NS	6(66.7)	3(33.3)			
	X	2(50.0)	2(50.0)			
	S	23(48.9)	20(42.6)	4(8.5)		
31-35	NS	1(12.5)	2(25.0)	6(62.5)		
	X		2(40.0)	3(60.0)		
	S	18(34.6)	19(36.5)	15(28.8)		
36-40	NS	2(11.8)	4(23.5)	10(58.8)	1(5.9)	
	X	2(15.4)		7(53.8)	4(30.8)	
	S	10(13.9)	12(16.7)	43(59.7)	7(9.7)	
41-45	NS	2(22.2)	2(22.2)	2(22.2)	3(33.3)	
	X	2(14.3)	3(21.4)	4(28.6)	5(35.7)	
	S	6(7.4)	14(17.3)	36(44.4)	25(30.9)	
46-50	NS		1(8.3)	6(50.0)	5(41.7)	
	X	1(8.3)		5(41.7)	6(50.0)	
	S	9(8.7)	13(12.6)	34(33.0)	42(40.8)	5(4.9)
51-55	NS	3(25.0)	1(8.3)	4(33.3)	2(16.7)	2(16.7)
	X	1(5.6)		4(22.2)	8(44.4)	5(27.8)
	S	9(10.1)	8(9.0)	24(27.0)	32(36.0)	16(18.0)
56-60	NS		2(14.3)	4(28.6)	4(28.6)	4(28.6)
	X	3(20.0)	3(20.0)	1(6.7)	1(6.7)	7(46.7)
	S	8(8.3)	3(3.1)	21(21.9)	36(37.5)	28(29.2)
61-65	NS			4(15.4)	6(23.1)	16(61.5)
	X			4(9.1)	18(40.9)	22(50.0)
	S	7(3.9)	1(0.6)	19(10.6)	53(29.4)	100(55.6)

Table 16 Correlations between Dust Variables

	Tot. Dust	(Tot. Dust)^2	Age wgt Dust	Time wgt Dust	Σ(Ann.Dust)^2	Dust wgt by yrs working	Dust wgt by calendar yr	# yrs more than 5mppcf	Dust in 1st 5 years	Yrs since 1st expos	Yrs of exp.	Peak Dus
Tot. Dust	1.000											
(Tot. Dust)^2	0.863	1.000										
Age wgt Dust	0.971	0.812	1.000									
Time wgt Dust	0.957	0.882	0.881	1.000								
Σ(Ann.Dust)^2	0.898	0.945	0.830	0.931	1.000							
Dust wgt by yrs working	0.909	0.765	0.921	0.858	0.758	1.000						
Dust wgt by calendar yr	0.977	0.803	0.984	0.873	0.824	0.896	1.000					
# yrs more than 5mppcf	0.709	0.413	0.730	0.608	0.429	0.732	0.745	1.000				
Dust in 1st 5 years	0.823	0.694	0.746	0.824	0.801	0.585	0.777	0.515	1.000			
Yrs since 1st exposure	0.494	0.264	0.484	0.494	0.303	0.565	0.468	0.603	0.365	1.000		
Yrs of exp.	0.499	0.266	0.489	0.486	0.288	0.534	0.481	0.611	0.362	0.918	1.000	
Peak Dust	0.841	0.603	0.799	0.802	0.739	0.728	0.823	0.613	0.809	0.472	0.455	1.000
Ave. Dust	0.950	0.779	0.941	0.856	0.839	0.822	0.968	0.685	0.825	0.393	0.372	0.839

The variables made up of various linear weightings of annual dusts tend to be correlated fairly highly with each other. The variables that are created from other information, such as years of exposure, years since first exposure, and peak dust are not correlated as highly as are the dust variables as a rule. However, high correlations are found between closely related variables such as years since first exposure and total years of exposure.

4.3. Response Scales

4.3.1. Descriptive Statistics

4.3.1.1. Response Scales

Descriptive statistics for the five response scales are presented below. A range of score is necessary to show any relationship between exposure and response.

Table 17 Descriptive Statistics for Response Scales

	Range	Standard Deviation	Median	Mean
Response 1	-170.67 - -20.84	16.55	-92.77	-91.70
Response 2	4.66 - 40.69	4.45	10.17	11.02
Response 3	0.0 - 3.167	0.345	0.00	0.104
Response 4	-12.0 - 0.0	4.66	-6.55	-6.36
Response 5	0.0 - 21.0	5.13	4.07	5.34

4.3.1.2.Components of Response 2

Descriptive statistics for each variable in Response 2 are presented below. This was done to determine whether the variation was contributed by all components of the scale or whether most of it came from one source. As Table 18 shows there was good variability on all components of the scale.

Table 18 Range of Scores on Components of Resp 2

	Range	Standard Deviation	Median	Mean
Q60	0.0 - 2.0	0.879	0.640	0.805
FVC	0.350 - 1.567	0.147	0.9376	0.9315
SRO	1.5 - 8.5	0.410	2.011	2.074
SIO	1.5 - 9.5	0.680	2.108	2.331

4.4 Results of Regressions

Results of the regression equations are presented in the following 5 sections. In Tables 19-23, beta refers to the standardized regression coefficient for the final regression equation with all the variables in the table. The correlation column gives the simple correlation between the response scale and that particular variable. The partial correlation gives the correlation for that variable as the last variable entering the final equation (ie. with all other variables in the

model). The p value gives the significance of the partial correlation.

4.4.1. Response 1 - Airflow Limitation

Three of the variables eligible for stepwise inclusion were significantly related to Response 1 at the p=0.1 level. These variables are dust weighted for years of residence in the lung, the sum of the annual dusts squared, and the average annual dust level. The coefficient for the sum of annual dusts squared is negative; the coefficients for the other two variables are positive. A summary of the regression results is given in Table 19.

Only two of the initial eight variables were still significant at the p=0.1 level after the stepwise variables were entered. Not surprisingly these were the smoking variables. For the purposes of the regressions, smoking was coded as: 0- non-smoker, 0.5- ex-smoker, and 1- smoker. The values of the smoking and smoking^2 variables will be the same for smokers and non-smokers. Smoking^2 would take a lower value than smoking for ex-smokers. For Response 1 the overall smoking effect is negative which could be predicted on the basis of the negative correlations between smoking and Response 1 in Table 5.

The overall association with the three significant dust variables is positive. The dust exposure profiles that the regression equation suggests are most strongly related to

Table 19 Correlation of Airflow Limitation (Resp 1) with Dust Variables

Variable	Beta	Correlation	Partial Corr.	P value
Age	0.3749	0.1988	0.0422	0.1600
$(Age)^2$	-0.2919	0.1964	-0.0336	0.2636
Total Dust	-0.0241	0.2252	-0.0025	0.9336
$(Total\ Dust)^2$	-0.0355	0.1119	-0.0096	0.7482
Smoking	0.4404	-0.1171	0.0733	0.0148
$(Smoking)^2$	-0.5111	-0.1407	-0.1048	0.0005
Smoking . Dust	-0.0517	0.1744	-0.0125	0.6766
Smoking . Age	-0.0902	-0.0080	-0.0180	0.5584
Variables entered stepwise				
Dust weighted for years of residence	0.4079	0.2055	0.0666	0.0267
Sum of $(Ann.\ Dust)^2$	-0.3883	0.1316	-0.0798	0.0080
Ave. Dust	0.2643	0.2169	0.0528	0.0791

response are ones that were received early on in a worker's career. High average (or short) dust exposures also seem to be a predictive factor. The sum of annual dusts^2 is weighted negatively. Workers who accumulated high dusts through high intermittent exposures would have nigher scores on this variable than those who accumulated the same total dust through steady but lower annual exposures.

Although the partial correlations for age and age^2 are not significant at p=0.1, the beta coefficients indicate that they are an important part of the final regression equation. The contribution of age is less than linear as the beta coefficient for age^2 is negative.

4.4.2. Response 2 Pulmonary Fibrosis

The relationship between dust variables and responses on this scale is of special significance because it includes the radiographic variables, SIO and SRO.

On the eight initially offered variables, only total dust has a significant partial correlation in the final equation. Two of the stepwise dust variables are related to Response 2, both negatively. The negative weightings of both the average dust and the sum of annual dusts^2 gives less weight to those total dusts accumulated by high exposures over a short period of time. Examples of this would be workers exposed to brief intense exposures and workers who have had "peaks" in their exposure profiles.

There is also evidence for an age effect. The relationship with age appears to be second order, as evidenced by the size of the absolute values of the beta coefficients for age and age^2. A summary of results is provided in Table 20.

4.4.3. Response 3 Pleural Fibrosis

The results for Resp 3 are summarized in Table 21. Pleural fibrosis shows some indication of an age effect that is between first and second order. There is scant evidence to suggest that pleural fibrosis is related to smoking. The correlations of either smoking or smoking^2 with pleural fibrosis are low, -0.0008 and -0.0055 respectively. The beta coefficients in the final regression equation are small, almost equal and of opposite sign.

The dust effect seems to indicate that two aspects of profile are of importance. The positively signed dust variables include two that would weigh early and long-term exposures more heavily. These are years since first exposure and dust weighted for years of residency in the lung. Two other variables seem to indicate a "peak" effect. These are the number of years with greater than 5 mppcf exposure and the sum of the (annual dusts)^2. The latter variable and the total dust squared both check for second order relationships between dust and response. However the two variables are slightly different. Two workers with the same total dust^2 may have quite different values for the sums of their annual

Table 20 Correlation of Pulmonary Fibrosis (Resp 2) to Dust Variables

Variable	Beta	Correlation	Partial Corr.	P value
Age	-0.0665	0.3651	-0.0075	0.7950
$(Age)^2$	0.2653	0.3677	0.0307	0.2901
Total Dust	0.6998	0.2592	0.1221	0.0000
$(Total\ Dust)^2$	0.0177	0.1494	0.0052	0.8569
Smoking	-0.1661	0.0905	-0.0277	0.3399
$(Smoking)^2$	0.1324	0.0880	0.0272	0.3488
Smoking . Dust	-0.0054	0.2534	-0.0013	0.9639
Smoking . Age	0.1335	0.2614	0.0267	0.3568
Variables entered stepwise				
Sum of $(Ann.\ Dust)^2$	-0.3526	0.1436	-0.0973	0.0008
Ave. Dust	-0.2525	0.2115	-0.0708	0.0148

Table 21 Correlation of Pleural Fibrosis (Resp 3) with Dust Variables

Variable	Beta	Correlation	Partial Corr.	P value
Age	-0.2907	0.2259	-0.0328	0.2856
$(Age)^2$	0.4287	0.2326	0.0494	0.1076
Total Dust	-0.6643	0.1014	-0.1063	0.0006
$(Total\ Dust)^2$	-0.2097	0.0359	-0.0653	0.0335
Smoking	0.0466	-0.0008	0.0078	0.8002
$(Smoking)^2$	-0.0406	-0.0055	-0.0083	0.7859
Smoking . Dust	0.1881	0.0927	0.0455	0.1379
Smoking . Age	-0.0479	0.1095	-0.0096	0.7551
Variables entered stepwise				
Years since first exposure	0.1239	0.2470	0.0698	0.0231
Dust weighted for years of residence	0.2514	0.1204	0.0545	0.0758
# of years with more than 5mppcf	0.1965	0.1733	0.0991	0.0013
Sum of $(Ann.\ Dust)^2$	0.3177	0.0682	0.0708	0.0211

dusts^2. The worker who has accumulated his exposure from alternating high and low levels will have a higher value for the sum of annual dusts^2 than a worker who has accumulated the same total exposure from steady annual exposures.

4.4.4. Response 4 Bronchitis

For this scale the highest beta coefficient is for smoking^2, as shown in Table 22. This is hardly surprising, as smoking has long had an association with bronchitis. Smoking itself is negatively signed and while it reduces the effect of smoking^2, the overall smoking effect remains. The higher weighting given to smoking^2 may indicate that ex-smokers are more like non-smokers than smokers with respect to their response on this variable.

Age and age^2 seem to play little effect. The same is true of total dust and total dust^2. The age weighted dust variable is heavily weighted, indicating that dust exposures occurring at later ages may be more harmful. The relationship of the other dust variables to response is a little more complicated. The variable, dust weighted for calendar year, weights recent dusts more heavily than those in the past. It differs from dust weighted for years of residence not only by a constant, but is opposite in sign as well. Dust weighted for calendar year, with its negative coefficient would act to reduce the dust weighted for age effect, as all workers get older with an increase in calendar year. The sum of the annual

Table 22 Correlation of Bronchitis (Resp 4) with Dust Variables

Variable	Beta	Correlation	Partial Corr.	P value
Age	0.2811	0.1353	0.0296	0.3303
$(Age)^2$	-0.2501	0.1327	-0.0263	0.3864
Total Dust	0.0735	0.1189	0.0086	0.7770
$(Total\ Dust)^2$	0.0899	0.0698	0.0256	0.3982
Smoking	-0.5369	0.2259	-0.0892	0.0034
$(Smoking)^2$	0.7023	0.2494	0.1438	0.0000
Smoking . Dust	0.0373	0.1540	0.0090	0.7670
Smoking . Age	0.0699	0.2640	0.0140	0.6455
Variables entered stepwise				
Dust weighted for age	0.5586	0.1380	0.0769	0.0115
Sum of $(Ann.\ Dust)^2$	-0.3119	0.0609	-0.0709	0.0197
Dust weighted for calendar year	-0.4571	0.1267	-0.0520	0.0867

dusts^2 enters the equation with a negative coefficient, reducing the effect of years of very high exposure.

4.4.5. Response 5 Airway Reactivity

The largest absolute value of a beta coefficient for the initially entered eight variables is 0.1836 for age. Other positive betas of note include -0.1672 for total dust, 0.1308 for smoking squared, and 0.1017 for the smoking age interaction.

Six stepwise variables were included in the equation. The sum of the annual dusts^2, and the number of years with more than 5 mppcf both have negative beta coefficents which may indicate that peak exposures are of less significance than steadier levels of exposure. The four positively signed variables are the dust in the first 5 years, dust weighted by the number of years working, the dust weighted by age, and the average dust. Complete results are provided in Table 23.

4.5 Correlations of Dust Variables with Response Scales

One interesting finding to come out of this study was that some of the individual dust variables were correlated with the response to a greater, or at least equal extent, than was total dust. Table 24 shows that for each of the response scales, dust weighted for years of working has a higher correlation than does total dust, although for some of the scales the correlations are almost the same. Two other variables

Table 23 Correlation of Airway Reactivity (Resp 5) with Dust Variables

Variable	Beta	Correlation	Partial Corr.	R value
Age	0.1836	0.2904	0.0201	0.4963
$(Age)^2$	-0.0081	0.2876	-0.0009	0.9758
Total Dust	-0.1672	0.2040	-0.0177	0.5508
$(Total\ Dust)^2$	0.0878	0.0973	0.0238	0.4212
Smoking	-0.0586	0.1696	-0.0098	0.7419
$(Smoking)^2$	0.1308	0.1660	0.0268	0.3660
Smoking · Dust	-0.0344	0.2148	-0.0083	0.7789
Smoking · Age	0.1017	0.2888	0.0203	0.4922
Variables entered stepwise				
Sum of $(Ann.\ Dust)^2$	-0.4543	0.1016	-0.0995	0.0008
Dust in first 5 years	0.2463	0.1817	0.0934	0.0017
# of years with more than 5 mppcf	-0.1142	0.2189	-0.0578	0.0510
Dust weighted by # of years working	0.1918	0.2116	0.0518	0.0802
Dust weighted for age	0.2150	0.2301	0.0380	0.1989
Average Dust	0.1428	0.2057	0.0340	0.2508

incorporating annual dust counts, dust weighted for age, and dust weighted for calendar year, do as well as or better than total dust in predicting response, as measured by the correlations in Table 24. Perhaps this is not surprising as they contain more information than does total dust alone. In addition to annual dust information they contain information on a worker's age or number of years working. More surprising is the finding that years of service and years since first exposure are the best single predictors of response. These variables do not contain any direct information on a worker's total dust exposure, but only on the time of exposure. However, all these variables are interrelated to some degree: total dust can only increase with time and vice versa. In general, those workers with the highest dust exposures will be the oldest and will have been working the longest.

Although it is tempting to take the correlations in Table 24 at face value, one must bear in mind that it is difficult to compare them without formal tests of significance.

Table 24 Correlation of Response Scales 1 - 5 with All Dust Variables

	Airflow Lim.	Pulm. Fib.	Pleural Fib.	Bronchitis	Air React.
Total Dust	0.225	0.259	0.101	0.119	0.204
(Total Dust)^2	0.112	0.149	0.036	0.070	0.097
Dust weighted for age	0.226	0.277	0.098	0.138	0.230
Dust weighted for yrs. of res	0.206	0.244	0.120	0.099	0.166
Sum of (Ann. Dust)^2	0.132	0.144	0.068	0.061	0.102
Dust weighted by # of yrs. working	0.229	0.298	0.116	0.135	0.212
Dust weighted for calendar yr.	0.227	0.256	0.082	0.127	0.221
# of years with more than 5mppcf	0.260	0.300	0.173	0.137	0.219
Dust in first 5 years	0.180	0.178	0.085	0.093	0.182
Peak Dust	0.222	0.223	0.105	0.084	0.197
Ave. Dust	0.217	0.212	0.069	0.110	0.206
Yrs. of service	0.234	0.340	0.218	0.101	0.230
Yrs. since first exposure	0.239	0.346	0.247	0.121	0.256

4.6 Overall r^2 for Regression Equations

Table 25 r^2 for Final Regression Equations

Var	r^2 (1st 8 var)	r^2 (final)	Stepwise Variables Added
Resp 1	0.1091	0.1148	Dust wgted for yrs res.
			Sum of (Ann. dust)^2
			Ave. dust
Resp 2	0.1594	0.1750	Sum of (Ann. dust)^2
			Ave. dust
Resp 3	0.0518	0.0768	Yrs since 1st exp.
			Dust wgted for yrs res.
			# yrs more than 5 mppcf
			Sum of (Ann. dust)^2
Resp 4	0.0887	0.0961	Dust wgted for age
			Sum of (Ann. dust)^2
			Dust wgted for cal yr.
Resp 5	0.1240	0.1400	Sum of (Ann. dust)^2
			Dust in 1st 5 yrs.
			# yrs more than 5 mppcf
			Dust wgted by # yrs work
			Dust wgted by age
			Ave. dust

Clearly the explanatory variables examined account for only a modest amount of the variability in the data.

Nevertheless, considering the wide range in individual's susceptibility and the necessarily crude estimations of dust exposures in the early part of this century, the correlations are as high as could reasonably be expected. In the present context, there appears to be no reason why these values, low as they are, cannot be used to explore the influence of differences in exposure profile.

5 DISCUSSION

5.1 Correlations of Resp 1-5 with Dust Variables

There are a number of ways of grouping the five response scales with respect to their relationships to the dust variables. Table 24 shows that the correlations for Resp 1-3 and 5 with the dust variables indicate a similar pattern. The two variables, years of service and years since first exposure, are always among the three highest correlations for these responses. If the dust variable, number of years with more than 5 mppcf, is also included, one finds that these three dust variables are always ranked in the highest five correlations. The magnitude of these correlations is also roughly the same with the exception of Resp 2 (Pulmonary Fibrosis). The correlations for Resp 2 are higher (approximately 0.34) than for the other three scales (which are approximately 0.23-0.25). Although it would be preferable to have higher correlations, those obtained are credible given the limitations of the data and the complexity of the responses. It is not surprising that the Resp 4 scale should stand alone with lower correlations and with a different pattern of correlations to the dust variables than did the other four scales. The lower correlations might be expected because bronchitis is related to more exposures than are pulmonary and pleural fibrosis.

One result that might not have been expected is the higher correlations for pulmonary fibrosis than for pleural fibrosis.

Both might be expected to show a fairly strong relationship to some measure of dust exposure. Pulmonary fibrosis showed the highest correlations but pleural fibrosis had correlations of the same magnitude as airflow limitation, and airway reactivity. The reason for the lower correlation with the dust variables for pleural fibrosis is consistent with past studies which have also found that pleural disease shows less of a dose-response relationship than parenchymal disease. This may be because other host factors enter into the production of pleural disease. For example, parenchymal disease may show a closer relationship to dust dose because it is initiated by a reaction of the body at the site of deposition. Pleural disease, on the other hand, may require the clearance of the dust from the initial site of deposition and its transport to a more peripheral location where the reaction would be initiated. This would provide one more way in which individual differences could manifest themselves and thus blunt the dose-response relationships.

The dust variables having the highest correlations with Resp 1-3 and 5 were all defined in terms of years rather than dust counts. At first glance one might be tempted to attribute this to factors other than the total dust exposure that would be contained in these terms; these factors might include age, a residence effect, or simply the fact that dust exposures were much higher in the past. These explanations are made less likely by the fact that variables that combine total dust and these effects generally had lower correlations than did years

of service, years since first exposure, or number of years of more than 5 mppcf. The difference in the size of the correlations is not great.

This finding may be of some use to future researchers as it is much more difficult to obtain and calculate total dust exposures for each worker than to simply look at the number of years he has been working, or the number of years since he has started working. Some studies have already used the number of years exposed as a measure of dose (1,59). This study adds support for this approach.

5.2 Discussion of Regression Results

The main objective of this study was to determine if any variables that describe profile of dust exposure would be significantly related to the development of a response after other explanatory variables such as age, cumulative dust, and smoking were taken into consideration. These results are discussed in the following sections, the results were presented in Tables 19-23.

5.2.1 Resp 1 Airflow Limitation

Of the eight variables initially entered into the regression, only smoking and smoking squared remained significant in the final equation. The beta coefficients are opposite in sign and the overall effect is that smoking is

negatively related to the exposure. At first glance this may seem a little incongruous. The result may be understood by recalling how Resp 1 was calculated. It is composed solely of the % predicted FEV; separate regression equations were used to derive the predicted FEV for smokers, non-smokers, and ex-smokers. The correlation of smoking with Resp 1 was negative which indicates that the use of separate regression equations in the calculation of % predicted FEV probably over corrected for the effect of smoking. This is probably because the people on whom the regression equation was based were not directly comparable to the men in this study.

Among the dust variables, only three: dust weighted for years of residence, the sum of the annual dusts^2, and the average dust, are significant predictors in the final equation. The sum of annual dusts^2 is negatively signed, the other two are positive. The overall effect seems to be that early exposures are weighted the most heavily and that the same overall amount of dust is more harmful when received as a steady exposure than it would be if received as a series of high exposures interspersed with lower exposures.

These features all fit with the conception of airflow limitation as a slow, progressive process. The earlier dust exposures are presumably more harmful because the retained dose (i.e. that fraction not removed by clearance mechanisms) has more time in the lung in which to exert harmful effects. The reason for the significance of average dusts is not as clear. This variable is very similar to total dust, but would give

more weight to an equal exposure obtained over a shorter period of time. It would be compatible with a quasi-threshold effect; low steady dust levels could be handled by the body's clearance mechanisms but above this level the body's clearance capability would be overwhelmed.

5.2.2 Resp 2 Pulmonary Fibrosis

The regression results for Resp 2 show that total dust is the largest single contributor to the equation. There is also evidence for an age effect, the relationship being better described by age squared than by age. The smoking age product has a beta of greater than 0.1, indicating that there is some interaction between smoking and age, with smoking exerting more of an effect in the elderly than in the young.

The two dust variables entered stepwise are both negatively signed. They may both be indicating the same effect, namely that for the same total dust, the dose that was accumulated in the shorter period with peaks and dips in the exposure pattern is less harmful than a long-term steady dose. This may be deduced by considering the values of the sums of the annual dusts squared for two workers with the same total dose by different profiles of exposure. For example, a worker whose total exposure is 100 mppcfy will have a sum of annual dust squared of 1000 if he accumulated that total by having an exposure of 10 mppcf for ten years. If the same total dose was accumulated by five years of exposure at 18 mppcf and five

years at 2 mppcf, the sum of the annual dusts squared would be 1646. Similarly it may be seen that the average dust score will be higher for workers who accumulate a given total dust through a short high exposure than for those who accumulate it through a lower but longer exposure.

The finding that total dust is the most important descriptor of dust exposure for those who develop pulmonary fibrosis should come as no surprise. This measure of exposure has been used in several studies in the past which use x-ray changes and mortality as response measures (49,54,56). This response scale included pulmonary x-ray changes similar to those used in previous studies. One might also expect that the x-ray changes included in Resp 2 would be more closely related to death from asbestosis than the responses included in the other scales.

5.2.3 Resp 3 Pleural Fibrosis

The regression for this scale yielded the lowest r^2 of the 5 scales. Similarly a look at Table 21 shows that the correlations between Resp 3 and all the predictor variables tend to be lower than for the other scales. Again this is consistent with past studies which have shown less of an association between dust exposure and pleural changes than for other parenchymal changes.

As Table 21 demonstrates, smoking has no relation to the development of pleural fibrosis. There is evidence for an age

effect that is more than linear but less than second order.

Dust exposure is related to pleural fibrosis, several of the descriptors of exposure profile were significantly related to Resp 3. With the inclusion of these variables in the stepwise section, the beta coefficients for total dust and (total dust)^2 are both negative. All four of the dust variables entered stepwise have positive beta coefficients and might be thought of as describing two profile effects. Years since first exposure and dust weighted for years of residence indicate that early exposures are more harmful. Whether this is due merely to the passage of time since the exposure or other factors is not clear. The other two variables, number of years with more than 5 mppcf and the sum of the (annual dusts)^2, describe a peak effect. The presence of both these variables indicates that very intense exposures over a brief period may be more harmful than the same total exposure spread over a longer period.

One might speculate that this is due to an overwhelming of the clearance mechanisms during periods of high exposure. Dust particles might not be cleared as completely, some of the particles transported to the lung periphery, but not removed might become trapped permanently and would, over time, be increasingly likely to trigger some pleural reaction.

5.2.4 Resp 4 Bronchitis

The greatest contribution to the regression equation for Resp 4 comes from smoking. This might have been expected from past studies and had the results shown otherwise doubts might have been cast on the validity of this study's methodology. Smoking squared provides a better fit than smoking. As already discussed, the two variables differ only in the value assigned to ex-smokers. Apart from the smoking effect there is little of importance in the first eight variables.

The three dust variables entered in the stepwise section were dust weighted for age, the sum of the annual dusts^2, and dust weighted for calendar year. The age weighted dust variable weights dusts received at older ages more heavily. Dust weighted for calendar year weights recent dusts more heavily than the early ones. Thus, to a certain extent, both both variables will weight the same dusts (i.e. for all workers more recent dusts occurred when they were older than they were when they received their earlier dusts). The opposite signs for the beta coefficients indicate that they cancel to some degree. The age weighted dust is more heavily weighted in the regression. The sum of the annual dusts squared has a negative coefficient, again indicating less of an effect for peak exposures than for the same cumulative dust obtained by a steadier profile.

5.2.5 Airway Reactivity

Of the eight initially entered variables only age, smoking^2, and the smoking age interaction had beta coefficients greater than 0.1. Total dust had a negative contribution to the final equation.

Among the stepwise variables the sum of the annual dusts^2 and the number of years with more than 5 mppcf both made negative contributions, the former more than the latter. The effect of both of these would be to weight peak exposures less than steady ones. The positively signed variables were dust in the first five years, dust weighted by number of years working, dust weighted by age, and the average dust. The beta coefficients for these variables range from 0.14-0.24. The dust weighted by age and by number of years working describe the same type of effect, namely that of weighting the recent exposures more heavily. This would seem to be an effect opposite to that expressed by the dust in the first five years. Weighting of recent dusts makes sense in that airway reactivity might be considered an acute, short-term effect of dust exposure. Perhaps the importance of dust in the first five years could be as a "sensitizer", exacerbating the effects of later dusts exposures. While it is tempting to speculate in this manner, the data are not sufficient to allow any firm conclusions on this question. Compared with the results for Resp 1-4, the results for Resp 5 are less clearcut, with more variables and lower beta coefficients.

5.3 Plausibility Of Dose Effects

The analysis in the preceding sections indicates that the effect of profile of dust exposure may vary with the response. Different responses have been shown to be associatad with certain aspects of exposure. To the extent that Resp 1-5 reflect markedly different pathological processes, the difference in the profile effects may be reasonable. Furthermore, the effects of profile for the various responses are consistent with what is known about the pathogenesis of those responses. The contribution of other explanatory variables such as smoking and age are also generally consistent with what is known about the clinical entities the various Resp scales attempt to describe. Examples of the plausibility of these dose effects may be drawn from the responses on any of the Resp scales.

5.4 Relationship of Findings to Past Studies

The results of the present study do not contradict the results of previous work. They confirm exposure response relationships that have been found in other studies which have looked at the relationship between dust exposure and non-malignant asbestos associated disease.

Dose-response in previous studies has been defined in terms of cumulative exposure (total dust) (49,54,56) or in

terms of years spent working with asbestos (1,57). As already discussed both have limitations. Table 24 shows that all Resp scales were correlated with cumulative (total) dust as well as with variables more akin to those used by Selikoff et al (years since starting work and total years of service). Although a comparison is not made between the two methods of estimating dose, Table 24 shows that both these ways of estimating dose can produce similar correlations with the five response scales.

The present study goes beyond just demonstrating an exposure-response relationship and tries to improve upon those established in past studies. To a limited extent the attempt has been successful. It has been demonstrated that for all the response scales there are additional variables which describe profile of dust exposure that are significantly related to response even after such variables as smoking, age, and cumulative dust have been taken into account.

5.5 Smoking Effect

The effect of smoking is of major importance in the study as it is associated with most of the response variables. Smoking effects were controlled in two ways in this study. Where possible, men's responses were adjusted to take into account their smoking status. This was only possible for pulmonary function responses. As already described, separate regression equations were used for smokers, non-smokers, and ex-smokers to derive a predicted value for a man's pulmonary

function test results. This adjustment is only of importance in Resp 1 and 2 because these were the only Resp scales containing a pulmonary function test.

In the case of Resp 1, the scale was made up solely of the pulmonary function variable. In Resp 2 the pulmonary function variable which was adjusted, was combined with x-ray and questionnaire variables which were not adjusted for smoking status.

The second method of taking into account a man's smoking status was to enter smoking, smoking squared, and the interaction terms smoke times dust and smoke times age into the final regression equations. These variables could not be deleted during the stepwise part of the program, ensuring that smoking variables would be in the final equation whether or not their partial correlations were significant.

The effect of smoking was probably adequately taken into account by these methods. In the case of Resp 1, where both methods were used, it appears that the standards used to correct for smoking which were based on another population, may have over corrected for the smoking effect. This may be demonstrated by the negative correlations of smoking and smoking squared with Resp 1, as well as the negative overall contribution that smoking made to the final regression. The situation with Resp 2 is not as clear cut. Here smoking does not appear to exert a great effect, although it may express itself through the smoking age interaction term. One cannot tell if this is due to the adjustment made for smoking in

calculation of predicted FVC or if there is a slight association partially eliminated by the treatment of FVC. It may be the latter as the correlation for Resp 2 with smoking and smoking squared is slightly positive (0.0905 and 0.0880) while that for Resp 1 is slightly negative (-0.1171 and -0.1407).

It might have been simpler not to combine variables that had been adjusted for smoking with those that had not. Originally, it was envisaged that pulmonary function variables would not be grouped with x-ray and questionnaire variables and the adjustments were based on this plan. However, after the initial factor analyses it became apparent that the present construction of Resp 2 was warranted.

The issue of how to make adjustments for smoking is not a serious one for this study as the objectives were only to describe the effects of profile of dust exposure on response and not to draw conclusions regarding the effect of smoking. For this study's purposes it is only required that sufficient adjustment be made for smoking so that it will not obscure dust effects or cause spurious ones to appear. The method used, while a little convoluted, attains these goals.

5.6 Difficulties with Study Design

Mention has been made in previous sections of some of the strengths and weaknesses inherent in the study design. These factors limit the strength and applicability of the study

results to some extent. The main defence for any inadequacy in the study design is that existing data were used and that this placed severe constraints on the study structure. Had the data been collected solely for this study many changes would have been possible. However, the extent of the data is such that it would have been impractical to collect them for anything less than a series of major papers.

Analysis of data generally proceeded without much difficulty. Extensive checking of data was carried out prior to any analysis to make sure that all variables were within range and that there were no missing data. As previously discussed a few men were deleted from the study for these reasons.

One further problem became apparent after the final regression analyses were run. It appeared that one man had been incorrectly coded for either his birth date or his year of starting work. The latter being coded as one year prior to the former, a clear impossibility. It was decided to print out his response scores as well as all his dust indices to examine whether or not he might have acted as an outlier and thus have exerted disproportionate influence on the regression results. Comparison of his scores with other men's scores revealed this was not the case. It was then decided to leave this man in the analysis on the grounds that one man out of 983, who was not an outlier, would not appreciably affect the results.

A further criticism may be made of this study with regard to the response scales. It was planned that the 5 scales

should reflect 5 different (and largely independent) responses to inhaled dust. As may be seen in Table 5 there is a correlation of 0.702 between Resp 2 and Resp 5; this is higher than was desired. The reason for the magnitude of the correlation is that Q60 (breathlessness) was included in both Resp 2 and in Resp 5. The inclusion of this question on both scales may be justified on clinical grounds; it is entirely reasonable that breathlessness be a symptom of pulmonary fibrosis and of airway reactivity.

Most of the descriptors of temporal patterns of exposure were obtained from weightings of annual dusts. This made computation relatively easy and allowed a variety of patterns to be examined. It is unsure how close these variables come to approximating the phenomena they are supposed to represent. For example, the dust weighted for years of residence, by itself may not capture the residency effect which may or may not exist in the data.

5.7 Implications for Hygiene Standards

This study has demonstrated that there are ways of calculating dust exposure other than, or in addition to, cumulative dust exposure that may help predict subsequent response. Whether or not the results have any relevance for current standards of exposure to asbestos is debatable.

There are many difficulties in trying to relate the experience of the men in the study to the situation of men in

the workplace today. First of all, the dust exposure in this study was almost entirely to chrysotile asbestos. The generalizability of the findings to other types of asbestos or non-asbestiform dust is unknown. Even if the results are only applied to current chrysotile workers there are difficulties in relating the dosages in this study to current exposure standards. First of all, the units of measurement used in this study are different from those used today and there is no way of obtaining a consistent conversion factor. A second problem is that the exposures of workers today are much lower than the vast majority of workers' exposures in this study. Whether or not the same effects of profile of exposure would be found at these lower overall levels of exposure is unknown. If they were, they might be so small as to make their detection very difficult. Another problem with applying the study findings to hygiene standards is that the outcomes used in this study do not reflect the most serious outcomes of asbestos exposure, at best the findings might be related to risk of death from asbestosis. The results do not necessarily have any relevance to asbestos-induced malignancy. It should be noted however, that in the past hygiene standards have been based on the risk of death from asbestosis only.

Bearing in mind all the above, it should be obvious that that this study's findings alone could not be used to justify the setting of an overall asbestos exposure standard. However, in conjunction with other evidence, this study's results might have been used to support further standards in the workplace

which would describe the short term exposure profile of the worker. If results had shown that brief intense exposures were more harmful than the same exposure received over a longer period, there might have been support for setting short term exposure limits and/or ceiling levels for asbestos exposure in addition to the present time-weighted average. In general, the results of this study do not indicate such an effect. Thus future changes in standards for asbestos exposure should revolve around lowering the present standard rather than adding other standards to modify the profiles of exposure permitted by the present standard.

6.0 CONCLUSIONS

In summary, this study has confirmed the known exposure-response relationship between cumulative asbestos exposure and several measures of respiratory morbidity. In addition, it has shown that some facets of the profile of asbestos exposure improve the prediction of subsequent response. With the inclusion of these terms, the original cumulative dust term may no longer be significant. Overall r's, even with these additional descriptors of profile of exposure are still rather low (0.30-0.45) and thus it seems that individual differences, unmeasured variables, and error still account for the major portion of the variance in the data.

The aspects of profile that influence response vary across responses. In general, for long term processes earlier dusts appear to have a greater effect and for short term, reversible processes the most recent dusts are more heavily weighted. In the case of airways reactivity both early and recent exposures are important. Exposure-response relationships for pleural disease seem less clear than for parenchymal disease.

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APPENDIX 1

Q52 Do you usually cough first thing in the morning (on getting up*) in the winter?

(Count a cough with first smoke or on first going out of doors. Exclude clearing throat or a single cough.)

*For subjects who work by night.

Q53 Do you cough during the day - or at night - in the winter? Ignore an occasional cough.

Q54 Do you cough like this on most days (or nights*) for as much as three months each year?

Q55 Do you usually bring up any phlegm from your chest first thing in the morning (on getting up*) in the winter?

(Count phlegm with the first smoke or on first going out of doors. Exclude phlegm from the nose. Count swallowed phlegm.)

Q56 Do you usually bring up any phlegm from your chest during the day or at night - in the winter?

Accept twice or more.

Q57 Do you bring up phlegm like this on most days or (nights*) for as much as three months each year?

Q58 In the past three years have you had a period of (increased*) cough and phlegm lasting for three weeks or more?

Q59 Have you coughed up blood?

Q60 Are you troubled by shortness of breath when hurrying up a slight hill?

Do you get short of breath walking with other people of your own age on level ground?

Do you have to stop for breath when walking at your own pace on level ground?

(Q60 is a composite of the above 3 breathlessness questions, the more positive responses the higher the score on Q60.)

Q61 Does your chest ever sound wheezing or whistling?

Q62 Have you ever had attacks of shortness of breath with wheezing?

Q63 Does weather affect your chest?