PREDICTORS OF OCCUPATIONAL SENSITISATION TO GRAIN DUST ALLERGENS AND CHANGES IN LUNG FUNCTION AMONG GRAIN MILL WORKERS IN CAPE TOWN

Mohamed Fareed Jeebhay

MBChB (Natal) DOH (UCT)

submitted to:

Faculty of Medicine, University of Cape Town

(in fulfillment of Masters of Philosophy (MPhil) Degree in Epidemiology)

February 1998

PREDICTORS OF OCCUPATIONAL SENSITISATION TO GRAIN DUST ALLERGENS AND CHANGES IN LUNG FUNCTION AMONG GRAIN MILL WORKERS IN CAPE TOWN

by

Mohamed Fareed Jeebhay
MBChB (Natal) DOH (UCT)

This thesis is submitted to the Faculty of Medicine, University of Cape Town in fulfillment of the requirements for the Masters of Philosophy (MPhil) Degree in Epidemiology.

I hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

I empower the University of Cape Town to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signed by candidate
Signature Removed

February 1998

DEDICATION

This thesis is dedicated to all the workers of South Africa. I have come to learn, know and appreciate your struggle and toil through working with you. Whether you work thousands of metres underground unearthing its mineral wealth to build our country; till the soil to bring forth food from the earth to still our hunger; or work in the factories night and day sewing the cloth that adorns our bodies, I remember you all. The effort involved in writing this thesis pales in comparison to your work. Your struggle and toil has and always will leave an indelible mark on this beautiful land we call South Africa.

A special tribute to those workers involved in the milling of flour for the making of bread - for what is more essential to life than the bread we eat?

- Nkosi Sikelel iAfrika -

ABSTRACT

Occupationally-related airway diseases, including asthma and chronic obstructive lung disease, have emerged as having substantial public health importance. The **aim** of this study was to identify the predictors of occupational sensitisation to grain dust allergens and changes in lung function among grain mill workers in Cape Town. There were two major **objectives** of the study. Firstly, to determine which of the following factors determine the distribution of serum ECP (eosinophilic cationic protein): age, gender, grain dust exposure, smoking status, atopy and sensitisation to workplace allergens. Secondly, to investigate the risk factors associated with the following outcomes: i) sensitisation to occupational allergens; ii) diagnosis of occupational asthma; iii) diagnosis of chronic obstructive airways disease; and iv) longitudinal changes in lung function. The risk factors studied included age, gender, smoking habits, occupational exposure, lung function status on baseline survey (1989), and allergic sensitisation assessed at follow up (1996). The **methods** employed involved a repeat measures cross-sectional design including a cohort followed up at different points over a seven year period. Survey instruments included a questionnaire, spirometry and allergy tests (phadiotop, RAST for wheat, rye, Lepidoglyphus destructor, Tyrophagus putrescentiae and Sitophilus granarius). The **results** indicated an association of grain dust with pulmonary function and allergic sensitisation to grain dust constituents. After adjusting for known confounders such as age, gender and smoking, significant associations were found between employment duration and both decrements in lung function and sensitisation to wheat grain. A decrement of 278 ml in FEV_1 and 328 ml in FVC was associated with occupational sensitisation to wheat (and rye). Increasing employment duration resulted in annual decrements of 18.3 ml in FEV_1 and 23 ml in FVC for every year employed. The odds for developing occupational asthma was only mildly elevated (OR=1.35) with increasing employment duration. Age, however, was found to be protective (OR=0.85). Although we were unable to demonstrate a relationship between across-week changes in lung function, at inception, and rapid longitudinal lung function decline, our findings suggested that longitudinal change was related to the degree of airway obstruction at inception. Sensitisation to grain dust allergens was also found to be an independent predictor for FEV_1 and FVC. The prevalence of sensitisation was the highest for wheat (26.4%), followed by Tyrophagus putrescentiae (22.6%), rye (21.7%), Lepidoglyphus destructor (15.1%) and Sitophilus granarius (15.1%). Sensitisation to wheat was highly correlated with sensitisation to rye ($r = 0.92$) and so were Lepidoglyphus destructor and Tyrophagus

putrescentiae (r = 0.85). Although a large proportion of the workforce (41.5%) were sensitised to occupational allergens, the prevalence of respiratory symptoms was between 15.6% and 23.9%. There were 16.7% of workers with health outcomes which fulfilled our criteria for occupational asthma. Atopic workers in our study had at least a nine-fold increased odds of becoming sensitised to grain dust allergens (OR: 8.9-74.7) and a two-fold increased odds of developing occupational asthma (OR=1.9-84.9). Furthermore, the study found that smokers had a twofold increased odds of becoming atopic, thereby placing them at greater risk of developing respiratory health problems. The mean ECP in this population was 15.4 ug/l (SD:2.5). Although 45.3% of the workers were atopic, it was not found to be predictor of elevated ECP levels. We were however able to demonstrate a significant association between ECP and sensitisation to grain allergens. Workers sensitised to wheat (positive RAST) had, on average, 1.78 ug/l higher ECP levels. The odds of having an elevated ECP (> 15 ug/l) increased by 2.9 for workers sensitised to wheat grain. In **conclusion**, the results of the study indicate that selection effects are in operation, demonstrating the health worker effect. The findings also suggest that across week reactions may be less sensitive than the across shift changes in predicting rapid longitudinal decline in lung function. While we were able to characterise the distribution of ECP according to exposure, we were however unable to define the temporal relationship between elevated between exposures, ECP and lung function outcomes due to limitations of the study design.

ACKNOWLEDGEMENTS

I would like to acknowledge and thank the people and institutions who have assisted in making this study possible.

Thank you to the workers at Premier Milling and the members of the Food and Allied Workers Union who requested the study to be done and the mill management for permission to conduct the study. A special thank you to Sr Amina Mia who assisted with administering the questionnaires and Hilton Donson with the spirometry. The collaboration of Dr Jenny Stark and Anna Fourie from the Immunology Department of the National Centre for Occupational Health who conducted immunology tests, as well as Prof Paul Potter and Magda Schinkel of the Allergology Unit at the University of Cape Town who assisted with the blood sample storage, is acknowledged. I am grateful to Lydia Caincross for the data coding, Rhoda Japhtas of ITS at the University of Cape Town for the data entry, and Kathy Welch of the Centre for Statistical Research and Consultation at the University of Michigan for assisting me with the data analysis. The prior work of Dr Max Bachmann and Prof. Jony Myers, presently in the Department of Community Health at the University of Cape Town, in initiating the study and collecting the first set of data is hereby acknowledged. Assistance of my wife, Razia, and colleague, Dr Rajen Naidoo, with the graphical presentations and layout is highly appreciated. The supervision and comments on aspects of the manuscripts by Dr Rodney Ehrlich of the Community Health Department at the University of Cape Town and Prof Tom Robins of the School of Public Health at the University of Michigan has been invaluable. Financial support of the Medical Research Council is also acknowledged.

I would like to thank the members of the Industrial Health Research Group, Judith Cornell, Peter Lewis, Danielle Edwards, Simphiwe Mbuli, Fareed Abdullah, Shuaib Manjra, Daleen Baker, Stacey Stent, Wendy Fourie and Sophia Kisting for their ongoing assistance in conducting this study through the years. A special thank you to my beloved wife, Razia who has been a source of great strength, support and encouragement in completing this thesis.

TABLE OF CONTENTS **PAGE NO**

TABLE OF CONTENTS **PAGE NO**

6. LIST OF TABLES AND ACCOMPANYING FIGURES

7. LIST OF FIGURES

8. APPENDICES

1. INTRODUCTION

Occupationally-related airway diseases, including asthma and chronic obstructive lung disease, have emerged as having substantial public health importance. Nearly 30% of chronic obstructive lung disease and adult asthma may be attributable to occupational exposure. Occupational asthma is now the most frequently diagnosed occupational respiratory disease in the United Kingdom and the United States. Trends reported by the programme of Surveillance for Work-related and Occupational Respiratory Diseases in South Africa (SORDSA) indicate that it is the second most common disease after pneumoconiosis.[1,2,3]

With increasing industrialisation in South Africa the potential exposure of workers to respiratory sensitisers is bound to increase, replicating the patterns seen in more industrialised nations. More detailed study is therefore needed to refine techniques for monitoring workers' health and the work environment and to develop effective and practical means for preventing work-related airways diseases in at-risk workers.

Although the relationship of occupational asthma and chronic obstructive lung disease to workplace grain exposure has been well documented, identification of sensitive indicators for early diagnosis and disease progression in the local setting needs further elucidation. This thesis sets out to examine, by way of an epidemiological study, the risk factors associated with lung function decline and occupational sensitisation to grain dust allergens among a group of grain mill workers in Cape Town.

1.1 Literature review - Health effects associated with grain dust

> "I think that millers ..... must be continually whitened by the floating particles of flour; the grain is ground into the finest powder and the flying particles fill the mill-house, so that, willy, nilly, the mouth, nostrils, eyes, and ears, in fact every part of the body is besprinkled with flour. I have known many to become asthmatic from this cause and finally lapse into dropsy." (Ramazinni, De Morbis Articum, 1713)

It is well-documented that exposure to grain dust increases the risk of respiratory disease, particularly **asthma, asthma-like syndrome (non-allergic bronchoconstriction)** and **chronic obstructive lung disease**. Other conditions known to be associated with exposure to grain dust include conjunctivitis, rhinitis, dermatitis, organic toxic dust syndrome and extrinsic allergic alveolitis.[4]

These conditions are the result of a multitude of allergens and bioactive materials present in the grain dust. These include the actual grain kernels and husk which contain vegetable protein, microflora, mites, weevils, animal matter eg. rodents, and bacterial endotoxins.[5]

The wide range of biologic activities of grain dust is mediated through different cell types. Experiments in animals have shown that extracts of grain dust are not inert. Grain has been reported to induce histamine release, activate the complement pathway, encourage neutrophil chemotaxis and stimulate lymphocytes. Environmental and host factors determine the manifestation of the clinical syndromes experienced by workers exposed to grain dust. For asthma-like syndrome and chronic obstructive lung disease the degree of dust exposure seems to be important, whereas for grain dust asthma host susceptibility factors play a more important role.[4]

1.1.1 Acute effects

1.1.1.1 Asthma

Grain dust asthma is defined as asthma due to sensitisation to grain dust or one of its components. A wide range of asthma prevalence (2% to 40%) has been documented among workers exposed to grain dust.[4]

The asthma due to grain dust is characterised by immediate, late or dual allergic responses and is known to be IgE-mediated. Sensitisation is not due to a single allergen but due to many components in the grain dust. It is important to note, however, that house dust mites are not found in grain dust.[6]

The following agents have been identified in causing asthma among grain workers:[7,8,9,10]

- Specific grain: Wheat, soybean, barley, rye, oats and maize
- Storage mites: Lepidoglypus destructor, Acarus siro, Tyrophagus and Glycyphagus destructor
- Grain weevil: Sitophilus granarius
- Fungi: Aspergillus, Cladosporium, Ustilago

There are 40 different wheat antigens that have been identified using crossed immunoelectrophoresis. The antigenicity and subsequent development of symptoms is dependent on various factors which include:[10]

- different components of wheat (the protein fraction, viz. globulin, gliadin and glutenin)
- alteration of the grain in the processing of the wheat
- cross-reactivity of different grain antigens (wheat and rye)
- route of exposure (ingestion of gluten in coeliac disease or inhalation of wheat in occupational asthma)

1.1.1.2 Asthma-like syndrome (non-allergic bronchoconstriction)

Asthma-like syndrome in grainworkers is characterised by acute changes in lung function (fall in FEV_1 >10% over a working shift) with or without respiratory symptoms. The syndrome has a prevalence in different studies of 3.9-11%. The pathophysiology is probably not due to the Type 1 allergic reaction, commonly found with high molecular weight antigens and believed to underlie most true grain-induced asthma. The histamine and leukotriene-releasing properties of grain dust may be responsible. These acute changes occur independent of the expected diurnal daytime decrease in normal healthy individuals.[4]

The acute reversible lung function changes were first demonstrated among grain elevator workers. An increase in airflow measures occurred during periods of low production activity, and a decrease after full restoration of the grain elevator activity. Significant dose-response relationships between dust exposure and across-shift lung function changes have been shown for FEV_1, FVC, MEF_{50} and MEF_{25}. The mean personal total dust concentration under these conditions ranged from 1.0-3.6

mg/m^3. No associations were found with age, duration of employment, smoking or atopic status. [11,12,13,14,15,16]

Studies done on grain workers in the port of Vancouver showed significant decreases in FEV_1 across-shift on Mondays and across the working week. In a subsequent study conducted on the same group of workers after 2.5 years significant correlation was demonstrated between annual FEV_1 decline and the across-shift and across-week changes in the baseline study. This was confirmed in a second follow-up study performed six years later where significant correlation occurred between the annual decline in lung function measures (FVC, FEV_1 and MMEF) and the cross-week changes shown in the baseline study. Baseline reactivity may thus be a useful predictor of which workers are likely to suffer significant lung function loss over time as a result of greater grain dust exposure.[17,18,19]

1.1.2 Chronic effects

The chronic health effects of exposure due to grain dust have been documented in a large number of cross-sectional prevalence studies. These studies show consistently that chronic exposure to grain dust can give rise to permanent irreversible lung damage. While most of these studies were done among grain elevator workers in North America, Europe and North Africa, two previous studies in South Africa (partially based on the present study cohort) added to this body of evidence.

All these studies showed that the prevalence of chronic respiratory symptoms was significantly higher among grain exposed workers when compared to a control group, after adjusting for age, height and smoking status. This occurred despite progressive reduction in dust levels found on the follow-up study. Increasing prevalence was associated with increasing concentrations of grain dust exposure among workers in Egypt. [20,21,22,23,24]

There are however few longitudinal studies that have studied the chronic health effects among grain workers.

In the first such study among grain elevator workers, the annual decline in FEV_1 and MMEF was greater for grain workers when compared to a control group after a 2.5 year follow-up period. This

decline was significantly correlated with age (>50 years) and smoking in both groups. The mean annual decline among smoking men older than 50 years of age was 78.1 (±90.3) for the grain workers and 20.1 (±63.1) for the civic workers. In addition, decline in lung function among the study group correlated with acute changes in lung function at baseline over the course of one work shift and working week.[18]

Another study of 267 Canadian workers who did not change their smoking habits over a period of six years showed the following host factors affecting longitudinal decline in lung function: age, smoking, cross-week changes during the initial study and non-specific bronchial responsiveness determined during the follow-up study.[19]

These studies were unable to demonstrate a correlation between decline in lung function and baseline lung function, presence of respiratory symptoms, atopic status or duration of exposure.

The latter study, using a nested prevalence case-control design, was able to show that those workers with the greatest decline in FEV_1 (10% of the study group), compared to the 10% showing the lowest decline in FEV_1, were exposed to significantly higher dust exposures in the baseline study. These findings were corroborated in a 12 year follow-up study among French workers where grain dust exposure was related to a decline in FEV_1.[25,26]

1.1.3 Environmental factors associated with lung function decline: dose-response relationships

Environmental factors such as the dust concentration and dust composition are important in the aetiology of grain-induced lung disease. The contribution of dust composition has been described above. A number of studies have also examined the relationship between current grain dust exposure and lung function impairment. Correy et al showed an inverse relationship between FEV_1 and current respirable dust concentrations. Other studies demonstrated a relationship between duration of employment and lung function impairment.[27,28,29,12]

Enarson et al followed a group of workers over a six year period and showed that those workers exposed to average dust levels above 5 mg/m^3 experienced a very rapid rate of decline in FEV_1, averaging 100 ml/year. The study by Huy et al showed that workers with an average exposure between 4-9 mg/m^3 were found to have lower values for FEV_1 and FVC when compared to grain workers exposed to less than 4 mg/m^3. In this study, annual declines in FEV_1 were 10.4 ml for exposure levels less than 4 mg/m^3, 20.7 ml for exposure levels between 4-9 mg/m^3 and 34.1 ml for exposure levels greater than 9 mg/m^3.[30,31]

The most recent initiative is the collaborative study between the Netherlands and Canada which combined data from previously mentioned studies. It showed that despite the exposure misclassification, healthy worker effects, differences in exposure levels, exposure characteristics as well as differences in sampling devices used to measure exposure, there was a moderate agreement in exposure-response relationships for FEV_1 between the studied industries. The magnitude of the effects however differed for the various grain industries, although the range of the exposure-response relations was small. The estimated FEV_1 lung function losses for the Dutch transfer elevators was 89 ml/year (mean dust level: 44.6 mg/m^3, SD 25.7) and 28 ml/year for the Canadian terminal elevator workers (mean dust level: 2.0 mg/m^3, SD 0.8). These figures were obtained after adjusting for age, height and pack-years of smoking.[32]

There have been a number of cross-sectional studies estimating age-adjusted annual changes in lung function for normal healthy adults in South Africa. White et al summarised these estimates for FEV_1 which ranged between 18-36 ml/year for men and 13-34 ml/year for women. Goldminers were estimated to experience an additional 7 ml/year decline and smokers another 8 ml/year for smoking 20 cigarettes per day.[33]

The estimates from longitudinal studies among grain workers suggest that cross-sectional studies suffer from considerable underestimation of the effect of exposure on FEV_1. This is due to a number of factors which include:

- extrapolation of effects to lower levels of exposure
- results from cross-sectional studies which suffer from selection effects viz. survivor bias have been used to create regression models
- attenuation of the exposure-response relationships due to errors in the variables used as proxies of exposure
- possible errors in the underlying model assumptions such as linearity of the dose-response relationship

It must however be noted that the direction of bias in the linear dose-response relationship may however be indeterminate.

Estimated dose-response relationships taking the above factors into consideration find that for a life-time exposure of 40 years, each additional 1 mg/m^3 TWA of inhalable grain dust leads to approximately 120 ml additional loss in FEV_1.[34]

It has also been shown in non-grain exposed population studies that an excess average lifetime decline in lung function of 100-500 ml are strong predictors of respiratory disease morbidity and mortality.[35]

1.1.4 Host factors associated with respiratory health effects due to grain dust

Whilst environmental factors play an important role in the chronic health effects observed with grain dust, host factors appear to be especially important in the development of occupational asthma. The following factors have been associated with the respiratory health effects due to grain dust:

a) Atopy

Atopy has been shown to be strongly associated with occupational asthma caused by high molecular weight agents. Its importance as a risk factor has been demonstrated in grain studies which show that most grain farmers with asthma caused by storage mites are atopic. Cross-sectional studies, however, have been unable to confirm a higher prevalence of atopy among grain workers than in comparison groups, most likely owing to selection effects such as the healthy worker effect or exclusionary employment procedures practiced in industry. Atopy does not appear to be a predictor of longitudinal decline in lung function, however.[36,37]

b) Smoking

The contribution of smoking is evident in most studies. These show that smoking grain workers have a higher prevalence of respiratory symptoms and lower lung function than non-smokers. Most studies have shown that the effects of smoking and grain dust on chronic lung function decline are additive. Synergistic effects on small airways function have been observed in workers who were exposed for less than five years. Smoking, however does not appear to be related to acute cross-shift decrements in lung function.[38,39,17]

c) Non-specific bronchial responsiveness (NSBR)

Some studies have suggested that non-specific bronchial responsiveness (NSBR) present among grain workers is a predictor of longitudinal decline in lung function. The factors that have been associated with higher NSBR include a lower baseline FEV1; atopy; presence of respiratory symptoms and cumulative exposure to grain dust.[40,30]

d) Pre-existing respiratory disease

Workers with respiratory diseases or symptoms at entry have been shown to have an increased risk of developing pulmonary effects after grain dust exposure. They are also more likely to leave the industry than healthy workers.[41,42,43,17]

e) Alpha-1-antitrypsin deficiency

The evidence for alpha-1-antitrypsin deficiency as a predisposing factor for chronic obstructive lung disease in grain workers is equivocal.[44,45]

1.1.5 Recent advances in immunological techniques for the diagnosis of asthma - the role of eosinophil cationic protein (ECP)

Asthma due to grain dust can be reliably diagnosed using conventional diagnostic techniques viz. symptom history questionnaires, serial peak expiratory flow rate (PEFR) monitoring, spirometry, assessment of non-specific bronchial responsiveness (NSBR) and immunological tests viz. skin prick tests or radioallergosorbent tests (RAST). A good correlation has been shown in some studies between an asthmatic response on challenge tests and immediate skin prick tests to grain dust extract. The RAST detects specific IgE antibodies in the serum of workers exposed to known allergens present in grain dust. Since the grain antigens are of high molecular weight, the RAST are highly sensitive and specific.[46,47]

These conventional tests are however unable to provide direct information about the underlying inflammatory processes until symptoms emerge. Hence, a simple and accurate blood test measuring the degree of inflammation in the airways would be helpful in improving the management of a person with asthma. Recently it has been suggested that eosinophilic cationic protein (ECP) could be used as a marker for airway inflammation, since ECP becomes elevated in the serum of patients with active asthma. This could be used as a biological risk marker for the development of asthma symptoms or

acute exacerbations after exposure to trigger factors. Hence it could serve to monitor both the disease progression and the response to therapy.[48]

ECP is one of several cytotoxic proteins secreted extracellularly by eosinophils subsequent to cell activation. It has been suggested that the extensive bronchial epithelial damage seen in asthmatic patients is caused by these eosinophil granule proteins.[49]

Data from in-vivo studies of a group of patients have computed a geometric mean of 4.4 ug/l with the upper 95th percentile at 11.3 ug/l. The authors, based on their experience, recommended that the cut-off level for reference values be set at 15 ug/l. Since ECP serum levels are highest during the early evening, timing of specimens becomes important in the interpretation of results.[50]

Eosinophilic cationic protein (ECP) has been found to be closely correlated with the following factors:

a) Airways inflammation

In the only occupational study of ECP documented thus far, subjects demonstrated an increase in ECP levels and developed a late asthmatic reaction after exposure to toluene diisocyanate (TDI). By contrast, there were no significant changes in serum ECP levels after exposure to TDI in the control group. These results suggest that eosinophils are 'activated' in subjects who develop a late asthmatic reaction after exposure. So, the late asthma reaction is closely correlated with recruitment of eosinophils releasing ECP in the serum.[51]

In a study by Wever et al which followed up adult chronic asthmatics over a six month period, patients with raised ECP levels needed much more corticosteroid treatment to relieve their acute exacerbations, despite being on inhaled corticosteroid therapy.[52]

This suggests that ECP levels in the peripheral blood may be a useful marker to monitor airways inflammation after exposure to trigger factors.

b) Allergen load

Serum ECP levels are higher with increased allergen exposure. This has been shown in asthmatic subjects moving from low altitudes (high allergen exposure) to high altitudes (low allergen exposure) where serum ECP levels closely paralleled allergen exposure. Serum ECP can thus also be used as a measure of the extent to which allergen avoidance results in decline of eosinophilic inflammation.[53]

c) Severity of asthma

It has been demonstrated in bronchoalveolar lavage that there is a direct correlation between eosinophil activation, assessed by ECP levels, and disease severity. This has also been shown in allergen challenge testing of symptom-free asthma patients with elevated ECP levels. Such challenges result in late asthma reactions of higher severity than in asthma patients with low serum ECP levels. Serum ECP levels may therefore correlate inversely with lung function.[54,55]

d) Efficacy of treatment

The study by Venge et al demonstrated that pre-treatment of subjects with budesonide (inhaled corticosteroid) prevented the development of exercise-induced asthma and also reduced ECP levels. Similarly, serum ECP levels are able to predict the outcome of treatment. Increasing dosage of steroids result in decreased ECP levels associated with improvement of asthma symptoms. On termination of treatment the levels rise again. In this way ECP may alert the clinician to the possibility of relapses in patients with poor compliance with steroid treatment.[56,57,58]

1.2 Historical background

The health of grain mill workers in Cape Town

The wheat flour milling industry in South Africa produces on average 2 million tonnes annually. Production is dominated by eight large companies. In the 1992-3 year, 32 large and four small mills were in operation, with a daily capacity of 10 680 tonnes. Most of the large companies have well-equipped mills using advanced technology in the grinding process and in finished products handling. The Chamber of Milling most recent figures indicate that approximately 6500 workers are involved in the milling of wheat nationally (Mr Zunkel, Chamber of Milling - personal communication). The Western Cape province is one of the major contributors to the grain output for the country.[59]

The health risks associated with grain dust among workers in Cape Town was first highlighted in an epidemiological study, conducted by Yach et al in 1985, among 582 workers employed in four grain mills. In this study, 37% of the workers fulfilled the criteria for occupational asthma. The diagnostic criteria used included the presence of chest symptoms (regular cough, expectoration, wheeze or chest tightness) and either a greater than 10% decline in FEV_1 over the working week or a FEV_1/FVC ratio of less than 0.70. It is evident that this 37% is quite high. This may be due to the broad definition used to categorise this group. While the definition was able to characterise those workers with airway obstruction, it did not differentiate between those with asthma, asthma-like syndrome and chronic obstructive airways disease. This meant that aetiological factors could not be studied in greater detail.[20]

This was the first time that the disease burden associated with grain dust exposure was studied in South Africa. The study concluded that this had important implications for the grain mill industry in South Africa since the legislation for dealing with the prevention of and compensation for occupational diseases was completely inadequate at the time. Occupational asthma was not regarded as a compensable occupational disease at the time.

Work continued in 1989 when a cohort of grain workers at a nearby grain mill in Salt River and its depot in Epping, were assembled by Bachmann and Myers for a cohort study. The study aimed to

gain more information about the long-term respiratory effects of exposure to grain dust. Study subjects were selected on who were still employed by the mill at the time. This constituted 67% of the original group that had been working at the mill in 1983. Spirometry techniques followed American Thoracic Society (ATS) guidelines as in the previous study. In this study of 224 full-time and permanent workers the prevalence of airway obstruction (FEV_1/FVC ratio less than 0.70) was found to be 14%. They also found that 8.4% of workers had evidence of acute airway obstruction (more than 5% decrease in FEV_1 over the working week) and 10.8% had reversible airway obstruction (more than 10% increase in FEV_1 after administering a bronchodilator). The lung function tests were conducted on the same day at the same time as the prior study by Yach et al. The study also demonstrated the healthy worker effect in that it found that those workers who had left the company after 1983 had a higher prevalence of symptoms than those who had continued working. There was however, no significant difference in lung functions between the "stayers" and the "leavers".[60,21]

Subsequent to the findings of this study a Health and Safety Agreement was signed between Premier Milling and the Food and Allied Workers' Union, whereby the respiratory health of workers would be monitored on a regular basis. At the same time the Industrial Health Research Group submitted recommendations to the company for improvements in preventive measures to minimise workers' exposure to grain dust.[61,62]

Workers in this grain mill were examined by Jeebhay et al in a survey two years later using the same spirometry equipment and techniques according to ATS guidelines as in the previous study. In this group of 191 full-time and permanent workers, 12.1% had evidence of airway obstruction (FEV_1/FVC ratio less than 70%). The slight decrease in the prevalence of airway obstruction between this survey and the previous one could be explained by possible selection effects viz, survivor bias operating. There were 5.8% of workers in this group who showed a decline of their FEV_1 by more than 10% since 1989. Among these workers, there were five who had previously been clinically diagnosed as having occupational asthma due to grain dust and another five workers with chronic obstructive airways disease.[63]

Between 1991 and 1993, due to restructuring in the company, the depot was sold to another company. As a result the depot workers could not be followed up in the subsequent epidemiological surveys conducted in 1993 and 1996.

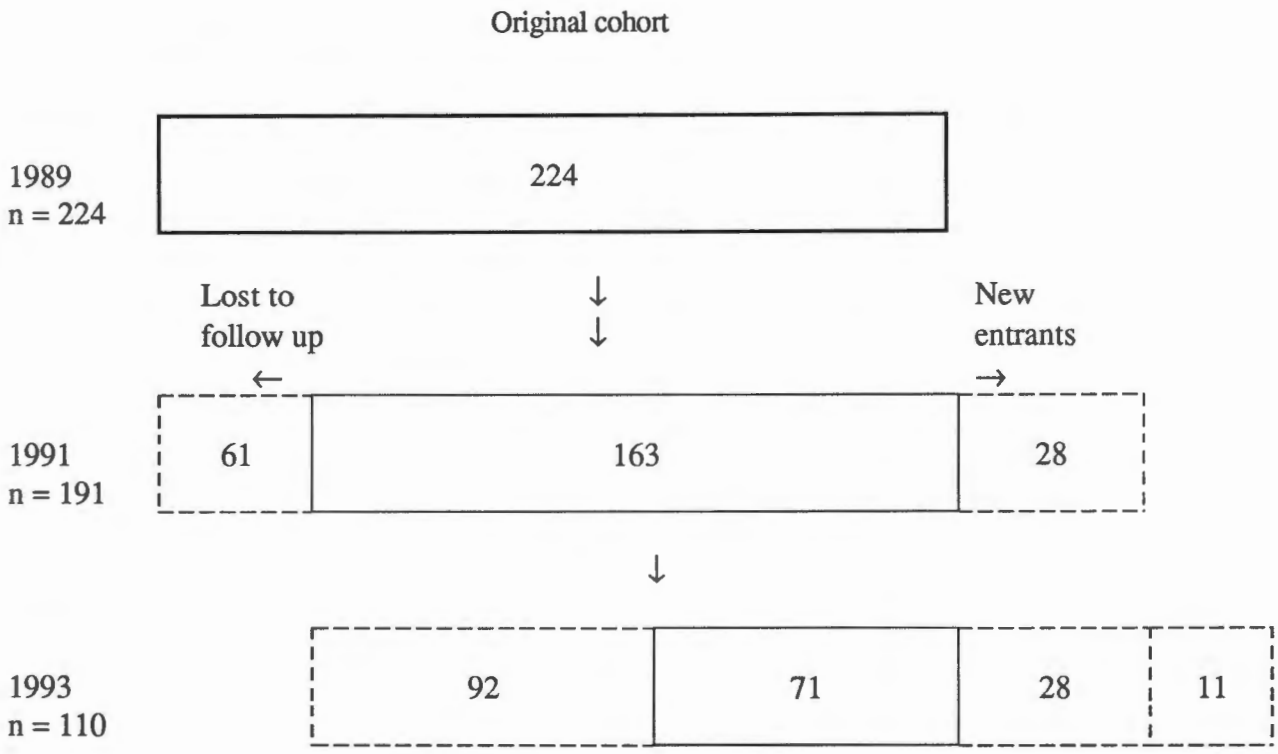
The survey conducted by the author at the mill in June 1993, using similar equipment and ATS guidelines, indicated that of the 110 workers screened, there were 11 workers (10%) with reversible airway obstruction and 21 workers (19%) with fixed airway obstruction (COAD). In further investigations of the 11 workers, the diagnosis of occupational asthma was confirmed by the author using allergy tests, flow-volume spirometry and clinical assessment, in six workers. The remaining five workers were categorised as having an asthma-like syndrome. This constituted an overall prevalence of occupational asthma of 5.5%, and a 19% prevalence of COAD. The allergens identified by radioallergosorbent tests (RAST) done on the serum of workers with occupational asthma were found to be positive for wheat, rye and storage mites (Lepidoglypus and Tyrophagus). None of the workers were sensitised to the alpha-amylase antigen usually present in flour dust. The compensation claims on behalf of these workers were submitted to the Compensation Commissioner. All six claims were subsequently certified as having occupational asthma.[64,65]

A preliminary analysis of the data on 71 workers belonging to the original cohort who had still been working at the mill failed to demonstrate a significant association between longitudinal decline in lung function and the following factors:

- age
- employment duration
- lung function tested at baseline (1989)
- acute changes in lung function (FEV_1 and FVC) across the shift at baseline (1989)
- response to B_2-agonist (FEV_1 and FVC) at baseline (1989)

The major limitation of this data was the very short period (4 years) of follow up of these workers which only provided three sets of consecutive lung function data for analysis. Furthermore, a substantial proportion of the 68.3% of workers had been lost to follow up, due to the internal restructuring and downsizing of the workforce in this company. The employment status of the workforce in the consecutive surveys are illustrated in Figure 1.1.[66]

Figure 1.1 The follow up history of the original grain mill worker Cohort in Cape Town



Trends in grain dust levels at the Salt River grain mill

The work processes in this grain mill can be broadly divided into two major operations located in physically separate locations. The first location houses all operations relating to production processes involved in the milling of the grain. The other location houses the clerical and administrative operations. The remaining description relates specifically to the actual production process occurring in the first location.

The wheat is transported to the mill from the various wheat farms by huge lorries. Upon arriving at the mill, the wheat is loaded off the lorries and stored in three silos. The general principle of the production process involves the moving of wheat stored high up in the silos in a downward direction utilising gravitational forces through various crushing and sieving processes to refine the wheat. The wheat is transported via chutes from the silos to the milling area. Here the wheat is milled into fine flour which then passes through another smaller system of chutes to the packing department. The flour is now in respirable form and has a high tendency to become airborne especially if there are major spills. Some workers are involved in cleaning up these spills using either vacuum cleaners or ordinary brooms. On reaching the packing department the flour is injected into paper packets of various sizes, sealed and then stored in the bag room. Forklift drivers load the bags or packs of flour onto the lorries for transport to the various bakeries in the town. A workshop is also present on site where the maintenance workers are involved in the fixing of vehicles or broken machinery. These workers have the potential to be exposed to excessive concentrations of dust released on opening up the machinery in the mill after a clogging up incident.

Bachmann et al documented in great detail the exposure profiles of the various jobs after a detailed survey conducted in 1989. These are presented in Table 1.1.[21,62]

Since 1989, the company commissioned another dust survey in 1996 upon request of the Department of Labour's inspectorate. This was subsequent to the Department of Labour being notified of the six workers with occupational asthma diagnosed at this mill. During that year some of areas in the plant had also undergone major structural changes. The results of the dust survey however indicated that the dust levels had not abated. It showed that the median dust concentration was 16.32 mg/m^3 (range:

4.84-27.23 mg/m^3). These values were higher than the measurements conducted in 1989 where the median concentration of personal dust samples was 2.41 mg/m^3 (range: 0.10-36.32 mg/m^3). In both surveys however, the packing department was still associated with the highest dust concentrations.[67,62]

This evidence indicated that workers involved in the milling of the grain dust at this mill were at risk of developing respiratory diseases such as asthma and chronic obstructive airways disease and therefore needed to be monitored on a regular basis. Hence, the ongoing medical surveillance of these workers was accordingly being done on a biennial basis using a standard protocol appended to the Health and Safety Agreement.

Figure 1.2 Dust exposure associated with different job categories among grain mill workers in Cape Town, South Africa, 1989

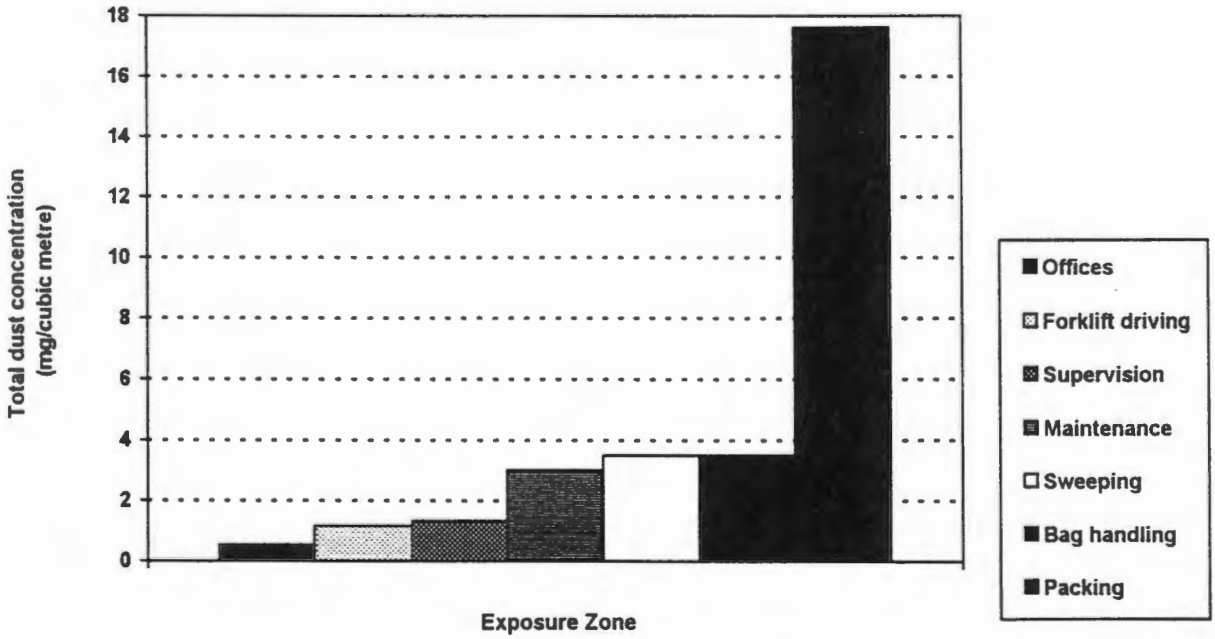


Table 1.1 Dust exposure associated with different job categories among grain mill workers in Cape Town (1989)

Exposure zone	No. exposed	No. sampled	Total dust conc (TWA) mean (range) mg/m^3
Office, laundry, canteen	37	6	0.53 (0.00-0.71)
Forklift, lorry drivers	24	8	1.16 (0.10-4.35)
Millers, silo and packing supervisors	10	4	1.34 (0.36-2.41)
Maintenance	9	4	3.02 (0.00-10.71)
Cleaners and sweepers	16	4	3.50 (0.43-7.70)
Bag handling	74	11	3.52 (0.57-8.69)
Shovel or pack grain	54	13	17.62 (0.81-95.59)
Total	224	50	6.10 (0.00-95.59)

Developments in occupational health and safety legislation with specific reference to workers exposed to grain dust

In the first half of this decade, major reform in occupational health and safety legislation occurred. During 1993 the two major laws pertaining to health and safety were repealed. The Machinery and Occupational Safety Act (MOSA) was replaced by the Occupational Health and Safety Act (OHSA) and the Workmen's Compensation Act (WCA) was replaced by the Compensation for Occupational Injuries and Diseases Act (COIDA).

The OHSA made it obligatory on all medical practitioners to report all cases of occupational diseases. Furthermore, the Regulations for Hazardous Chemical Substances (HCS) promulgated in 1995 under the OHSA required regular environmental monitoring and medical surveillance of workers at risk of developing health problems as a result of exposure to respiratory sensitisers. The HCS Regulations however, set the 8-hour time-weighted average (TWA) occupational exposure limit for grain dust (control limit) at 10 mg/m^3 total inhalable dust while classifying grain dust a respiratory sensitiser. This level is considered to be unacceptably high by international standards. The USA exposure standard mandates an 8-hour Threshold Limit Value (TLV) of 4 mg/m^3 whilst a report recently by a Dutch expert committee recommended an occupational exposure limit of 1 mg/m^3 8-hour TWA.[68,69,70,34]

In 1993 occupational asthma was included for the first time in the schedule of occupational diseases under the WCA, thereby making this disease compensable under South African law. The current legislation places the onus on employers to report occupational diseases to the Compensation Commissioner within 14 days of receiving notice thereof. This means that a worker with occupational asthma now has recourse to a social insurance system which ensures medical cover, and remuneration of 75% of loss of earnings as a result of the occupational disease for a period of two years. Permanent disablement benefits are calculated according to the criteria mentioned in Table 1.2. A score is assigned to both functional loss and the necessity for medication. The percentage permanent disablement is then assessed according to the total score as it appears in Table 1.3. The compensation payment is based on the percentage permanent disability and the wages of the worker. It takes the form of a lump sum payment if the percentage disability is below 30% and a monthly pension if it is more than 30%.[71,72,73]

Table 1.2 Pulmonary disability criteria and scores for occupational asthma used by the Compensation Commissioner in South Africa

FEV1	Score	Medication	Score
>80% of predicted	0	Nil	0
71 to 80% of predicted	1	One or more drugs	1
56 to 70% of predicted	2	(including inhaled steroids)	
40 to 55% of predicted	3	Systemic steroids	4
<40% of predicted	4		

Table 1.3 Permanent disability grading for occupational asthma used by the Compensation Commissioner in South Africa

Total score	Permanent disability %
6 to 8	100
5	80
4	60
3	45
2	35
1	25
0	15

1.3 Purpose of undertaking this research

In the light of the failure of recent structural improvements at the plant to reduce dust levels, and the new legal obligations required by the Regulations for HCS under the OHSA, the results of the medical surveillance programme are important in monitoring the containment of work-related respiratory problems.

Although the relationship of occupational asthma and chronic obstructive lung disease to workplace grain exposure has been well documented, identification of sensitive indicators for early diagnosis and disease progression in the local South African setting needed further elucidation.

The purpose of this study was to identify the risk factors for allergic sensitisation to occupational allergens and rapid lung function decline among workers over a seven year period. This information would enable practical recommendations to be made to modify the existing protocol for the medical surveillance of these grain mill workers. Furthermore, it was hoped that the study would stimulate the development of administrative and engineering controls and procedures to prevent further morbidity due to grain dust exposure.

1.4 AIM OF THE STUDY

To identify the predictors of lung function decline and occupational sensitisation to allergens present in grain dust among grain mill workers in Cape Town.

1.5 OBJECTIVES

1.5.1 To determine the prevalence of occupational asthma and chronic obstructive airways disease.

1.5.2 To determine the distribution of serum ECP (eosinophilic cationic protein) among grain workers and to identify whether the following factors are associated with elevated levels of ECP:

- age
- gender
- exposure to grain dust
- smoking status
- atopy
- sensitisation to workplace allergens

1.5.3 To investigate the risk factors associated with the following outcomes:

1) Sensitisation to occupational allergens
2) Diagnosis of occupational asthma
3) Diagnosis of chronic obstructive airways disease
4) Longitudinal changes in lung function

The risk factors include:

- Age
- Gender
- Smoking status and pack-years smoking
- Occupational exposure
    - employment duration
    - job type and dust exposure category
    - cumulative dust exposure
- Allergic sensitisation assessed *at follow up (1996)*
    - atopy
    - eosinophilic cationic protein (ECP) levels
    - occupational allergen sensitisation
- Lung function status on *baseline survey (1989)*
    - degree of airway obstruction (FEV_1/FVC ratio)
    - acute changes in lung function over a working week
    - response to B_2-agonist

2. METHODS

The protocol was reviewed and passed by the Ethics and Research Committee of the Medical Faculty of the University of Cape Town.

2.1 Study design

This is a repeat measures cross-sectional design including a cohort followed up at different points over a period of seven years.

2.2 Population and sampling

In March 1989, 224 workers at the Salt River grain mill and its Epping depot in the Cape Town metropolitan area participated in a cross-sectional survey. The survey was repeated in March 1991 (n=191), June 1993 (n=110) and December 1996 (n=111). Between 1989 and 1993, due to restructuring in the company, the depot was sold to another company, resulting in two large scale retrenchments of workers in 1990 and 1992. The criteria used to retrench workers was not known, but it is likely that the "last in first out" principle was used . A large number of these workers lived in the Ciskei and Transkei and therefore could not be traced. As a result these workers could not be followed up in the subsequent epidemiological surveys conducted in 1993 and 1996. Furthermore, the company was unable to provide records in such a form that an inception cohort could be studied. This group of workers was therefore excluded from the longitudinal analysis since no data was collected on these individuals during the latter two surveys. Hence, only 68 grain mill workers of the original cohort were still working in 1996. This is illustrated in Figure 2.1.[62,63,64]

This study, in an attempt to answer a number of questions and to make optimal use of the data collected throughout this seven year period had two major components:

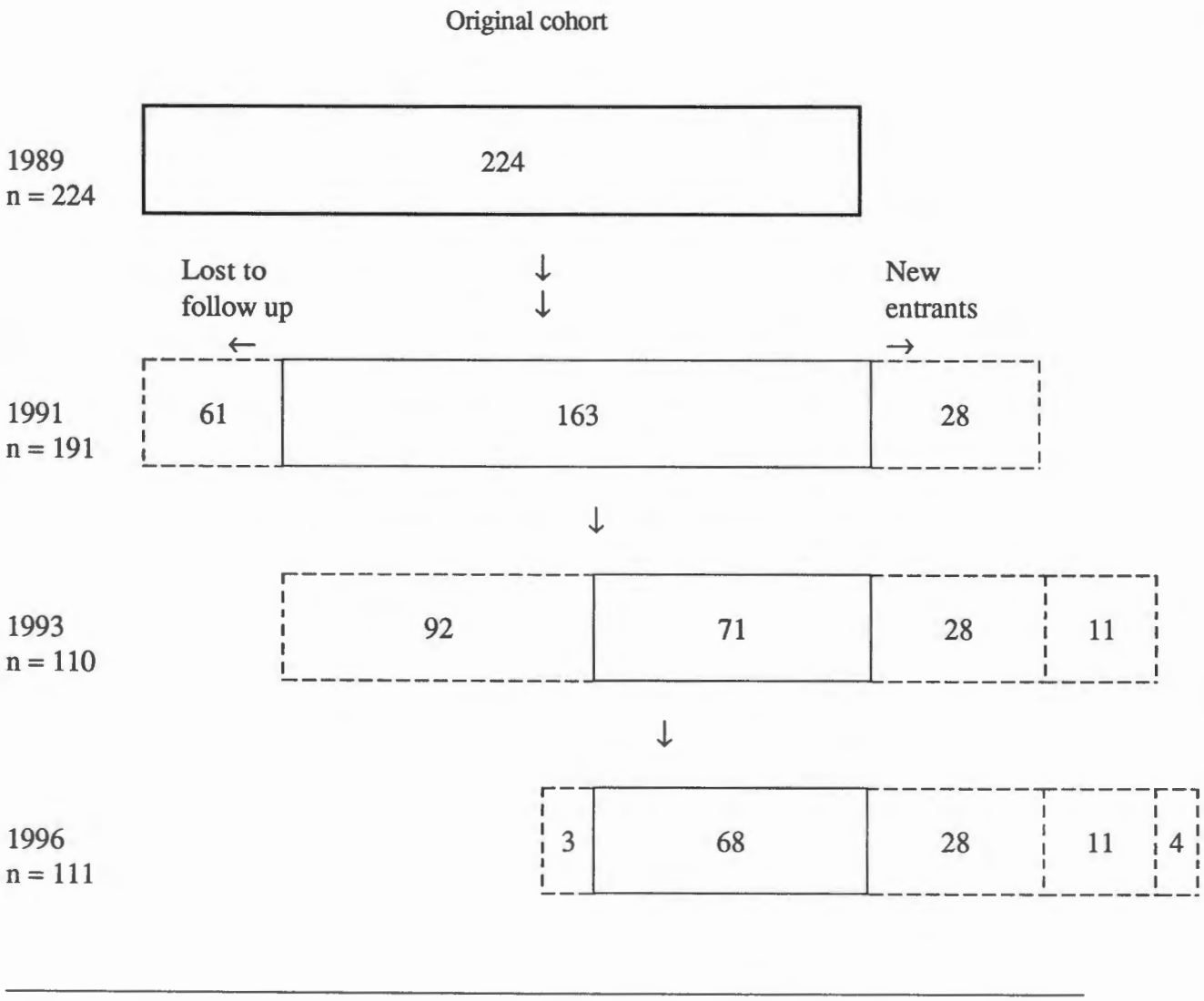
2.2.1 Cross-sectional analysis

The population under study for the cross-sectional prevalence data analysis constituted the currently working group (n=111). This included all workers who had been employed at the mill during the time of the 1996 survey. The focus of this analysis was to determine the prevalence of asthma and chronic obstructive lung disease, and to identify predisposing factors for elevated ECP levels among this group of workers.

2.2.2 Longitudinal analysis

This analysis focused on the predictors of allergic sensitisation, occupational asthma diagnosis and lung function decline among the grain mill workers. It included those workers who had been examined during the 1989 cross-sectional study and who were still currently working at the time and had participated in the 1996 survey. The advantage of studying this cohort is that data was available for a seven year period of follow up.

Figure 2.1 The follow up history of the original grain mill worker Cohort in Cape Town



2.3 Measurement instruments

2.3.1 Questionnaire

Each worker answered a standard respiratory questionnaire which contained questions relating to current and previous employment, degrees of exposure to grain dust and tobacco smoke, acute and chronic respiratory symptoms, and previous medical illnesses. The questionnaire was based on that of the American Thoracic Society (ATS), slightly modified for local conditions. The same questionnaire was used in all four surveys. The questionnaire was administered by trained interviewers in a language in which the worker was fluent.[20,74,21]

Smoking status was classified into three categories viz. non-smoker as lifelong abstinence from smoking; ex-smoker if ceased smoking completely more than a year before the survey; and current smoker if the person smoked any amount of tobacco in the past year.

2.3.2 Clinical examination

The clinical examination of the respiratory system was classified as abnormal if any of the following chest signs were present viz. crepitations, wheeze or rhonchi, or any other adventitious sounds.

2.3.3 Spirometry

The same Vitallograph S model bellows volume-time spirometers, meeting American Thoracic Society (ATS) guidelines for spirometers, were used in all four surveys. Spirometers were calibrated at least once a day with a three litre syringe and did not require adjustment as both spirometers had identical accurate readings. Spirometry was conducted in a standard way according to ATS guidelines by technologists who had undergone training in standard technique. Spirometry was performed in a sitting position without nose clips. Each worker performed up to seven trials to produce three acceptable curves.[21,75]

Start of the exhalation was determined by back extrapolation, which has been shown to bring such spirometers into compliance with ATS criteria. Where exhalation continued after the end of the chart had been reached, FVC was read from the maximum excursion of the spirometer stylus. The technologists watched each procedure to detect fluctuation of the stylus in the case of nose breathing and it was not necessary to reject any traces for this reason.[21,76]

The lung function indices included forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) for each subject. Tests were supervised by the technologists and quality control was strict. Test reproducibility was used as a guide to whether further attempts were necessary. Acceptable tracings for both FEV_1 and FVC were allowed to vary by no more than 100 ml or 5%, whichever was greater. The best FEV1 and FVC were used regardless of whether they belonged to the same tracing. Lung volumes obtained by spirometry were adjusted to body temperature and pressure according to the average temperature and pressure for each session.[21,77]

There were 4 workers (3.6%) who were unable to perform the tests due to poor coordination of effort and whose results were therefore not reported on in the 1996 survey.

The timing of the spirometry was done during the working day. In the first survey (1989) spirometry was done on three occasions viz. Monday mornings (48 hours after the last shift); Thursday afternoons (after 4 shifts of work); and again on Thursdays at least five minutes after inhalation of two puffs of a self-administered B_2-agonist (rimiterol) metred dose inhaler. In the subsequent surveys (1991, 1993, 1996), spirometry was done at the end of the week (usually on a Thursday) on two occasions viz. before and at least 15 minutes after inhalation of a self-administered B_2-agonist (ventolin) metred dose inhaler.[63,64,21]

Change in pulmonary function was measured for each subject over the survey week in 1989. Change in FEV_1 occurring over the working week was expressed as a percentage as follows:

$$\Delta\ FEV_1 = FEV_1 \text{ on Thursday} - FEV_1 \text{ on Monday}$$

$$\Delta\ FEV_1\ \% = \frac{\Delta\ FEV_1}{FEV_1 \text{ on Monday}} \times 100$$

In addition, change was measured over the 7 year period using the Thursday afternoon readings for each survey. Longitudinal change in lung function (FEV_1, FVC) was expressed as an annual change by computing the slope of the four readings obtained for each worker across the seven year period. There were 63 workers (93%) among the 68 "stayers" at the end of 1996 who had acceptable lung function tests that were reported on.[78,19]

The reference values used for the interpretation of spirometry readings were those proposed by the European Community for Coal and Steel.[79]

2.3.4 Immunology tests (done in the 1996 survey)

Informed consent was sought prior to any investigations being performed on any of the workers. A blood sample (6 ml) was drawn from each worker during the working week. A Becton Dickinson Vacutainer SST tube (with gel medium and clot activator was used. The blood was allowed to clot for 1-2 hours at room temperature (20-24 degrees Celsius). The sample was then centrifuged at 1350g for 10 minutes at room temperature at the Allergology Unit, UCT Medical School. The serum was then transferred to another tube and stored at -20 degrees Celsius until assayed for further measurement.

The analysis of the samples was conducted by the Immunology Department at the National Centre for Occupational Health. The technologist was blinded with regard to the exposure history of the specimens. While conducting the analysis for one allergy marker, the technologist did not have the results of the other markers in that batch.

The Pharmacia UNICAP machine was used to analyse the specimens using the Pharmacia CAP RAST kits (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). The allergens included:

- **Phadiotop inhalant screen:** common airborne allergens viz. House dust mite (HDM), Grassmix, Mouldmix, Dog dander, Cat dander, Bermuda grass, Aspergillus, Alternaria, Cladosposrium, Penicillum

- **Specific allergens:** wheat (F4), rye (F5), grain weevil viz. Sitophilus granarius (Ri202) and storage mites viz. Lepidoglyphus destructor (d71) and Tyrophagus putrescentiae (d72)

The **ECP** was measured by radioimmunosorbent assay (RIA) using Pharmacia kits (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden) according to the manufacturer's instructions.

There were five workers (4.5%) who refused the blood tests either for religious or other personal reasons.

2.3.5 Dust exposure classification

The workplace inspection and industrial hygiene survey indicated that workers were mainly exposed to various forms of wheat, ranging from raw grain to fine flour, as well as various biological and chemical contaminants. Three indices of exposure were used:

a) Employment duration in the mill.
b) Dust concentrations in the most recent job
c) Cumulative dust exposure

This was computed as the sum of the products of the duration in each job in this mill by the dust concentration of that job. This is presented in the formula below:

Cumulative Dust Exposure	=	employment duration in current or previous jobs	×	mean dust concentration per job type
	=	$(Job_1 \times Conc_1) + (Job_2 \times Conc_2) + J_n,C_n$		

For the latter two indices, the results of the 1989 hygiene survey was used as a basis for the dust concentrations. This is reflected in Table 2.1.[62]

It should be noted that although a repeat survey had been done by a private consultant for the company in February 1996, the results obtained for the old section of the mill were much higher than the previous survey. This could not be due to the recent silo which had been built in 1996 as one would have expected lower levels. These results were therefore not used for various reasons. Firstly, the survey did not cover all job types as in the previous survey. Secondly, the exposure sampling methodology following internationally recognised methods was not followed as in the previous survey. This resulted in some of the results being reported for static sampling rather than for personal sampling as reported for the first survey. It could therefore be concluded, since different sampling methodologies were used and the validity of the second one was in question, the 1989 total dust levels is a conservative estimate of the true exposure experience of these workers.[67,80]

Table 2.1 Dust exposure associated with different job categories among grain mill workers in Cape Town (1989)

Job Type	Total dust conc (TWA) mean (range) mg/m^3
Office, laundry, canteen	0.53 (0.00-0.71)
Forklift, lorry drivers	1.16 (0.10-4.35)
Millers, silo and packing supervisors	1.34 (0.36-2.41)
Maintenance	3.02 (0.00-10.71)
Cleaners and sweepers	3.50 (0.43-7.70)
Bag handling	3.52 (0.57-8.69)
Shovel or pack grain	17.62 (0.81-95.59)
Total	6.10 (0.00-95.59)

2.4 Data Management

2.4.1 Cross-sectional analysis

The following operational definitions were used for the outcome variables in the cross-sectional analysis:

a) Occupational asthma

The presence of any two of the following features:
i) Self-reported symptoms viz. wheeze with or without attacks of shortness of breath
ii) Increase in FEV1 greater than and equal to 12% after bronchodilator administration
iii) Positive RAST to any of the following antigens: wheat, rye, grain weevil, and storage mites (L destructor, T. putrescentiae)

b) Chronic obstructive airways disease

The presence of all three of the following features:
i) Self reported symptoms of cough and phlegm expectoration for more than three months in a year
ii) FEV1/FVC ratio < 0.70
iii) Does not have occupational asthma according to criteria in (a) above

c) Occupational allergic sensitisation

Positive RAST to any one of the following antigens: wheat, rye, grain weevil, and storage mites (Lepidoglyphus destructor and Tyrophagus putrescentiae)

2.4.2 Longitudinal analysis

The following outcome variable was measured for the longitudinal analysis:
- annual longitudinal change in lung function (ml/yr) as measured by the slope across the seven year period

2.4.3 Independent variables

- age
- gender
- height (standing)
- smoking status (and duration in pack years)
- employment duration (years)
- dust exposure concentration (mg/m^3)
- cumulative dust exposure (mg/m^3-yr)
- eosinophil cationic protein (ECP) levels (ug/l)
- presence of atopy at follow up exam (positive phadiotop)
- initial lung function (FEV_1/FVC ratio)
- acute changes in lung function over a week shift at baseline examination
- lung function response to B_2-agonist at baseline examination

2.5 Data Analysis

Analysis of the data was done using the SAS statistical packages for univariate, bivariate and multivariate analysis for the outcomes in relation to the predictors of interest. The distributions of cumulative exposure, dust concentrations per job category and ECP were highly skewed and were transformed logarithmically before testing.

The exposure indices variables viz. cumulative exposure, employment duration and dust concentration per job category were divided into quartiles to study the effects of increasing exposure on change in FEV_1. To minimise for confounding by age, pulmonary function parameters were considered as the percentage of predicted in the initial analysis. The cumulative exposure was divided into four quartiles (0-12.5 mg/m^3-yrs; 12.6-36.1 mg/m^3-yrs; 36.2-95.1 mg/m^3-yrs; 95.2-388.7 mg/m^3-yrs). Similarly, employment duration was also divided into four quartiles (0-6.9 yrs; 7-15.9 yrs; 16-20.9 yrs; 21-36 yrs). Dust concentration levels were divided into three categories viz. low

(<2mg/m^3); medium (2-4 mg/^{3}) and high (>4 mg/m^3). This was done in order to assess whether the assumption of linearity was reasonable prior to conducting the linear regression models. Of the three exposure indices, employment duration on its own was found to best represent relationship between exposure and FEV_1.[81]

Associations between exposure variables (exposure status, smoking status) and health outcomes (respiratory symptoms and immunological status) was investigated by means of Mantel-Haenszel Chi-Square Test for trend (Exact Test) and multiple logistic regression for categorical outcomes. Pearson's Correlation Coefficient, analysis of variance (Tukey's Studentised Test) and multiple linear least squares regression were used for continuous health outcomes (lung function and ECP levels).

Multiple linear regression analyses were conducted, adjusting for known confounders such age, gender, height (standing), smoking status (current, ex) and pack-years of cigarette smoking when assessing effects on lung function. Previous dust exposure or previous history of TB were not found to be significant confounders. Age, height, pack-years, employment duration, dust concentration, cumulative exposure and ECP were entered as continuous variables. Gender, current smoker, ex-smoker, phadiotop, elevated ECP (>15 ug/l), RAST for wheat (rye), Lepidoglyphus destructor (Tyrophagus putrescentiae) and Sitophilus granarius were represented by dummy variables (0,1). It must be noted that since very high correlation coefficients were found between wheat and rye as well as between Lepidoglyphus destructor and Tyrophagus putrescentiae, only the former of each pair mentioned was used in the regression models.

Since employment duration was found to have the strongest association with percentage FEV_1 predicted and also had the highest r^2 when compared to the other two indices of exposure it was included in each model relating to lung function indices. Models were also run to investigate whether occupational sensitisation i.o.w positive RAST for wheat (rye), Lepidoglyphus destructor (Tyrophagus putrescentiae) or Sitophilus granarius was able to independently predict FEV_1. This was in order to assess whether these markers could be regarded as independent markers for allergic sensitisation or whether they were merely indirect surrogates of exposure. Since wheat persisted, and

its p-value remained unchanged in the models with or without employment duration and dust concentration, it was considered to be an independent predictor of FEV_1.

For ECP, models were run independently with wheat, rye, Lepidoglyphus destructor and Tyrophagus putrescentiae as predictors. Based on obtaining the most significant p-values from these models wheat and Lepidoglyphus destructor variables were found to best describe the relationship with ECP.

All other variables were selected by a simple forward stepwise procedure (p for inclusion <0.1). If removal of the variable resulted in a change in the coefficient for employment duration greater than 10%, then the covariate remained in the model. Interaction terms were also used in the logistic regression model to ascertain if there were any effect modifiers. The model fit was evaluated by examining residual plots for outliers.

3. RESULTS

Characteristics of the workers

The personal characteristics of the entire workforce surveyed during 1996 are presented in Table 3.1, stratified according to employment duration. Most of the workers (89%) were men and almost half of the workforce were smokers at the time. The mean age of the workforce was 44.8 years. A large proportion (55%) of workers had worked in previously dusty occupations with an average duration of 5.5 years (SD:5.15). The age, height, weight and the proportion of workers with previous dust exposure (eg. mines, foundries, other grain mills) were however similar between the various employment duration categories. There were however some noticeable differences among female representation in the longer employment duration categories. This is related to the small number (11%) of females who had participated in the study.

Table 3.1 Demographic characteristics of grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

		Employment duration (yrs)			
	Total (n=111)	1st Quartile (0-6.9 yrs) (n=27)	2nd Quartile (7-15.9 yrs) (n=27)	3rd Quartile (16-20.9 yrs) (n=28)	4th Quartile (21-36 yrs) (n=29)
Age (yr)	44.8 ± 9.5	35.5 ± 9.2	44.8 ± 7.8	45.6 ± 6.3	52.89 ± 5.1
Gender: no. (%)					
- Males	99 (89%)	21 (77.8%)	23 (85.2%)	27 (96.4%)	28 (96.6%)
- Females	12 (11%)	6 (22.2%)	4 (14.8%)	1 (3.6%)	1 (3.4%)
Height (cm)	171.5 ± 7.4	171.2 ± 9.2	171.3 ± 7.7	171.6 ± 6.1	171.8 ± 6.9
Weight (kg)	77.4 ± 15.1	74.4 ± 18.4	77.0 ± 14.6	78.5 ± 12.7	79.4 ± 14.5
Exposure in current job (yr)	9.4 ± 7.4	2.9 ± 2.0	8.2 ± 4.7	12.5 ± 6.6	13.8 ± 8.9
Exposure in mill (yr)	14.5 ± 8.8	3.0 ± 2.1	11.1 ± 2.8	17.8 ± 1.5	25.4 ± 3.7
Cumul. exposure (mg/m^3-yr)	33.5 ± 4.4	6.7 ± 3.6	37.7 ± 3.7	47.7 ± 3.0	96.1 ± 2.3
Previous exposure: no. (%) (mining, foundries, mills)	61 (55.0%)	13 (48.1%)	16 (59.3%)	16 (57.1%)	16 (55.2%)
Smoking status: no. (%)					
- Current	54 (48.6%)	14 (51.9%)	13 (48.1%)	14 (50.0%)	13 (44.8%)
- Ex	32 (28.8%)	5 (18.5%)	6 (22.2%)	12 (42.9%)	9 (31.0%)
- Non	25 (22.5%)	8 (29.6%)	8 (29.6%)	2 (7.1%)	7 (24.1%)
Pack years (yrs)	15.1 ± 11.9	10.9 ± 11.0	15.4 ± 12.0	17.1 ± 11.9	16.5 ± 12.6

Note: Continuous variables - mean ± S.D.; Categorical variables - number (%)
For Cumulative exposure: Geometric mean ± S.D.

Prevalence of symptoms

Chest symptoms (any one of regular expectoration, cough, wheeze or chest tightness) occurred in 15.6% to 23.9% of workers (Table 3.2). A relatively low proportion of workers (5.5%) had symptoms of regular expectoration and cough (for at least three months per year for two years) suggestive of chronic bronchitis. While trends of increasing symptom prevalence were demonstrated for chest tightness and wheeze with and without breathlessness, as employment duration increased, only chest tightness showed a significant trend across categories ($p<0.05$). This trend persisted only for chest tightness when stratified according to smoking status, but was not significant (Table 3.3). Besides the expected trend of an increasing proportion of workers with previous treatment for asthma across ascending exposure categories (as categorised according to duration of employment), this was also observed for tuberculosis ($p<0.01$).

Table 3.2 Prevalence (%) of symptoms among grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

		Employment duration (yrs)			
	Total (n=109)	1st Quartile (0-6.9 yrs) (n=27)	2nd Quartile (7-15.9 yrs) (n=26)	3rd Quartile (16-20.9 yrs) (n=27)	4th Quartile (21-36 yrs) (n=29)
Cough	17 (15.6%)	2 (7.4%)	5 (19.2%)	6 (22.2%)	4 (13.8%)
Phlegm	18 (16.5%)	2 (7.4%)	6 (23.1%)	5 (18.5%)	5 (17.2%)
Chronic bronchitis	6 (5.5%)	1 (3.7%)	1 (3.8%)	2 (7.4%)	2 (6.9%)
Breathlessness	10 (9.2%)	0	3 (11.5%)	3 (11.1%)	4 (13.8%)
Tight chest	20 (18.3%)	3 (11.1%)	2 (7.7%)	7 (25.9%)	8 (27.6%)*
Wheeze	26 (23.9%)	5 (18.5%)	4 (15.4%)	7 (25.9%)	10 (34.5%)
Wheeze and breathlessness	9 (8.3%)	0	2 (7.7%)	3 (11.1%)	4 (13.8%)
Previous treatment for:					
- Hayfever	11 (10.1%)	5 (18.5%)	2 (7.7%)	1 (3.7%)	3 (10.3%)
- Asthma	8 (7.3%)	0	2 (7.7%)	3 (11.1%)	3 (10.3%)
- Tuberculosis	13 (11.9%)	0	3 (11.5%)	1 (3.7%)	9 (31.0%)**

Mantel-Haenszel Chi-Square test: * p-value < 0.05; ** p-value < 0.01

Table 3.3 Prevalence (%) of symptoms among grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status

		Smoking status		
	Total (n=109)	Current (n=53)	Ex (n=31)	Non (n=25)
Cough	17 (15.6%)	10 (18.5%)	2 (6.3%)	5 (20.0%)
Phlegm	18 (16.5%)	10 (18.5%)	5 (15.6%)	3 (12.0%)
Chronic bronchitis	6 (5.5%)	4 (7.4%)	1 (3.1%)	1 (4.0%)
Breathlessness	10 (9.2%)	4 (7.4%)	5 (15.6%)	1 (4.0%)
Tight chest	20 (18.3%)	12 (22.2%)	7 (21.9%)	1 (4.0%)
Wheeze	26 (23.9%)	14 (25.9%)	9 (28.1%)	3 (12.0%)
Wheeze and breathlessness	9 (8.3%)	6 (11.1%)	3 (9.4%)	0
Previous treatment for:				
- Hayfever	11 (10.1%)	5 (9.3%)	2 (6.3%)	4 (16.0%)
- Asthma	8 (7.3%)	3 (5.6%)	4 (12.5%)	1 (4.0%)
- Tuberculosis	13 (11.9%)	6 (11.1%)	5 (15.6%)	2 (8.0%)

Figure 3.1 Prevalence (%) of symptoms among grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

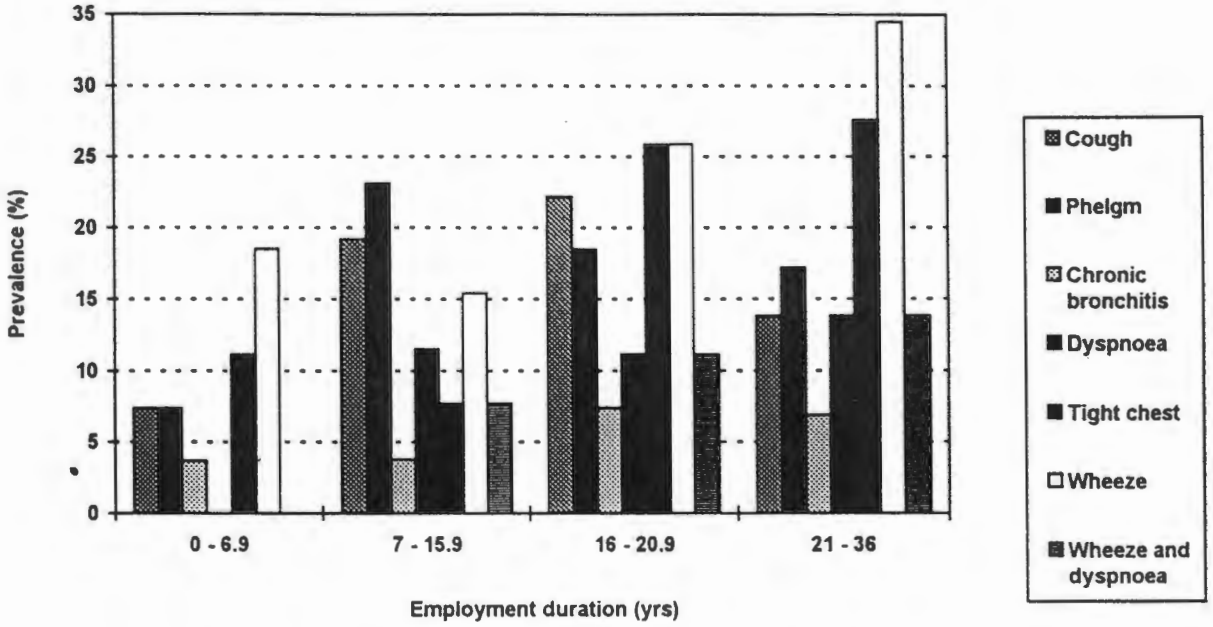
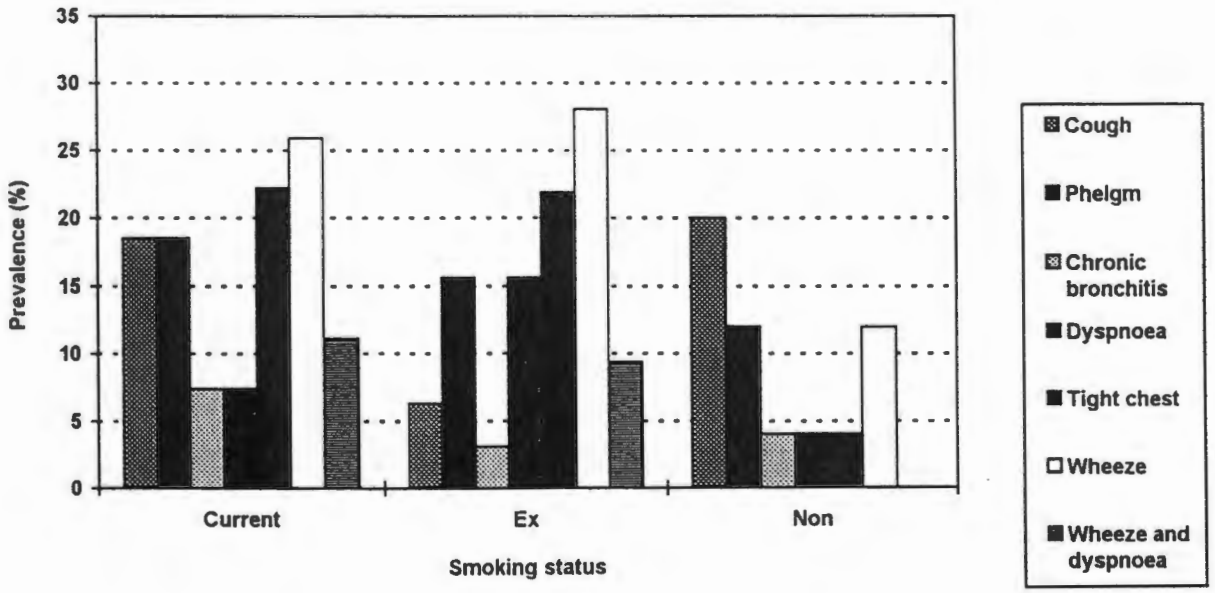


Figure 3.2 Prevalence (%) of symptoms among grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status



Pulmonary function tests

All three indices of lung function were related to exposure status for males and females demonstrating decreasing FEV_1, FVC and FEV_1/FVC ratio with increasing duration of employment (Table 3.4). This association was however significant for males only since the numbers of females were too few to provide enough statistical power to demonstrate a difference. These trends were less apparent when the lung function indices were expressed as a percentage predicted, suggesting confounding by age, gender and height. When stratified by smoking status, trends of declining lung function persisted with increasing smoking status for males (Table 3.5). The FEV_1/FVC ratio was significant even after expressing it as a percentage predicted ($p<0.05$).

Furthermore, when the outcome variable was expressed as the number (%) of workers with airway obstruction (FEV_1/FVC ratio < 70%) and stratified according to employment duration and smoking status, these trends were more apparent with increasing employment duration. Both associations however were statistically significant for employment duration ($p<0.001$) and smoking ($p<0.05$). Trends for significant airway reversibility (FEV_1>12% post bronchodilator administration) when stratified for either smoking status or employment duration showed confusing variation in prevalences which were not easily interpretable.

Table 3.4 Pulmonary function findings among grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

		Employment duration (yrs)			
	Total (n=107)	1st Quartile (0-6.9 yrs) (n=25)	2nd Quartile (7-15.9 yrs) (n=27)	3rd Quartile (16-20.9 yrs) (n=27)	4th Quartile (21-36 yrs) (n=28)
Males: (n=96)					
FVC (litres)	4.34 ± 0.88	4.78 ± 1.02	4.36 ± 0.88	4.38 ± 0.73	3.97 ± 0.78**
FEV_1 (litres)	3.33 ± 0.82	3.90 ± 0.84	3.34 ± 0.74	3.33 ± 0.69	2.89 ± 0.74***
FEV_1 / FVC	76.6 ± 10.1	82.2 ± 8.2	77.0 ± 7.6	76.1 ± 8.8	72.7 ± 12.5**
FVC % predicted	98.3 ± 16.2	100.9 ± 17.0	97.6 ± 17.8	100.5 ± 14.7	95.0 ± 15.8
FEV_1 % predicted	91.9 ± 17.7	98.7 ± 15.4	91.2 ± 16.1	93.4 ± 16.3	85.9 ± 20.5
FEV_1 / FVC % predicted	96.9 ± 12.1	101.5 ± 8.9	97.4 ± 9.5	96.4 ± 11.0	93.5 ± 15.9
Females: (n=11)					
FVC (litres)	3.81 ± 0.68	4.26 ± 0.49	3.53 ± 0.71	3.52 ± 0	2.97 ± 0
FEV_1 (litres)	3.19 ± 0.62	3.51 ± 0.45	3.07 ± 0.71	2.94 ± 0	2.27 ± 0
FEV_1 / FVC	83.5 ± 5.1	82.4 ± 5.2	86.8 ± 4.1	83.0 ± 0	76.0 ± 0
FVC % predicted	112.4 ± 11.9	116.3 ± 10.4	114.4 ± 11.6	-	-
FEV_1 % predicted	109.0 ± 15.2	110.7 ± 12.7	115.5 ± 14.9	-	-
FEV_1 / FVC % predicted	102.3 ± 5.4	100.1 ± 4.9	106.8 ± 3.7	-	-
Entire group: (n=107)					
No. with FEV_1 / FVC ≤70%	20 (18.7%)	1 (4.0%)	4 (14.8%)	6 (22.2%)	9 (32.1%)δδδ
No. with ≥12% increase in FEV_1 on salbutamol	4 (3.8%)	1 (4.0%)	1 (3.7%)	2 (7.4%)	0

Note: Continuous variables - mean ± S.D.; Categorical variables - number (%)
Reference values are from the European Community for Coal and Steel (ECCS), 1993
ANOVA: ** p-value < 0.01; ***p-value < 0.001
Mantel-Haenszel Chi-Square test: δδδp-value <0.001

Table 3.5 Pulmonary function findings among grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status

		Smoking status		
	Total (n=107)	Current (n=52)	Ex (n=31)	Non (n=24)
Males: (n=96)				
FVC (litres)	4.34 ± 0.88	4.38 ± 0.78	4.35 ± 0.94	4.24 ± 1.03
FEV_1 (litres)	3.33 ± 0.82	3.27 ± 0.79	3.38 ± 0.89	3.40 ± 0.80
FEV_1 / FVC	76.6 ± 10.1	74.7 ± 11.1	77.0 ± 9.5	80.8 ± 6.6
FVC % predicted	98.3 ± 16.2	99.3 ± 14.7	97.9 ± 16.9	96.5 ± 18.9
FEV_1 % predicted	91.9 ± 17.7	90.1 ± 16.7	92.8 ± 19.8	94.7 ± 17.0
FEV_1 / FVC % predicted	96.9 ± 12.1	94.3 ± 13.4	97.5 ± 11.4	102.3 ± 7.2*
Females: (n=11)				
FVC (litres)	3.81 ± 0.68	3.82 ± 0.77	4.81 ± 0	3.60 ± 0.51
FEV_1 (litres)	3.19 ± 0.62	3.25 ± 0.69	3.67 ± 0	3.02 ± 0.61
FEV_1 / FVC	83.5 ± 5.1	84.8 ± 2.2	76.0 ± 0	83.6 ± 6.70
FVC % predicted	112.4 ± 11.9	112.1 ± 10.5	125.0 ± 0	110.1 ± 14.1
FEV_1 % predicted	109.0 ± 15.2	110.4 ± 10.9	110.7 ± 0	107.3 ± 21.2
FEV_1 / FVC % predicted	102.3 ± 5.4	103.3 ± 2.0	95.7 ± 0	102.6 ± 7.6
Entire group: (n=107)				
No. with FEV_1 / FVC ≤70%	20 (18.7%)	14 (26.9%)	5 (16.1%)	1 (4.2%)δ
No. with ≥12% increase in FEV_1 on salbutamol	4 (3.8%)	2 (3.9%)	0	2 (8.3%)

Note: Continuous variables - mean ± S.D.; Categorical variables - number (%)
Reference values are from the European Community for Coal and Steel (ECCS), 1993
ANOVA: * p-value < 0.05
Mantel-Haenszel Chi-Square test: δpvalue < 0.05

Figure 3.3 Pulmonary function findings among male grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

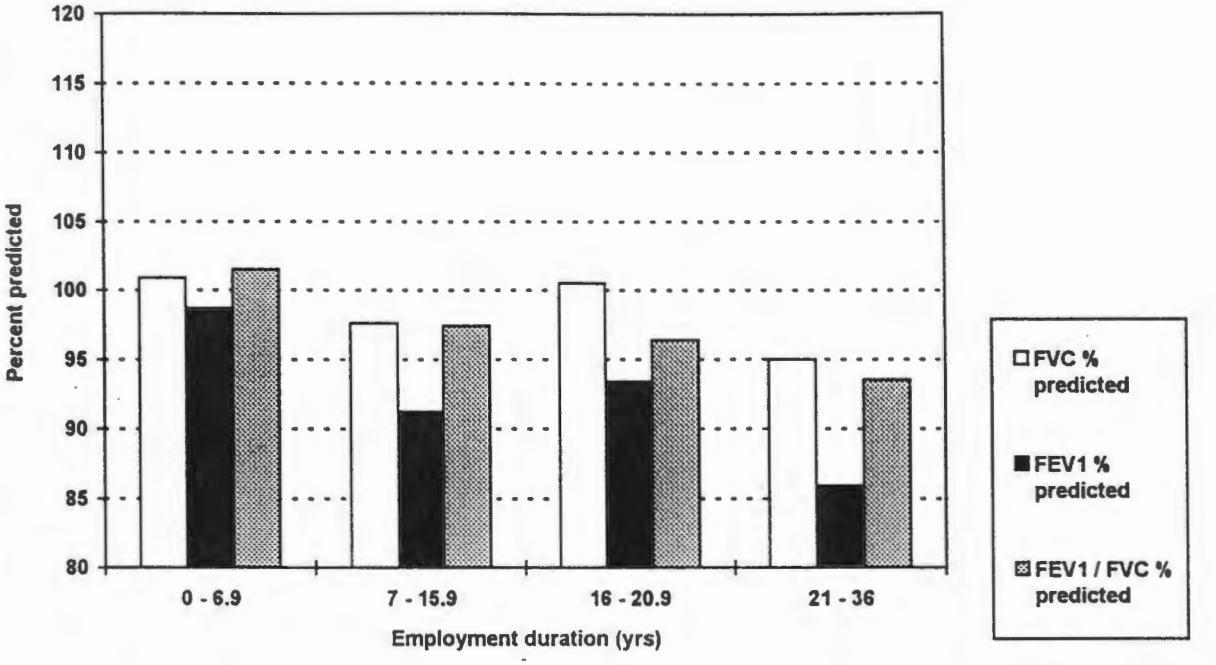


Figure 3.4 Pulmonary function findings among male grain workers in Cape Town, South Africa, 1996, stratified according to smoking status

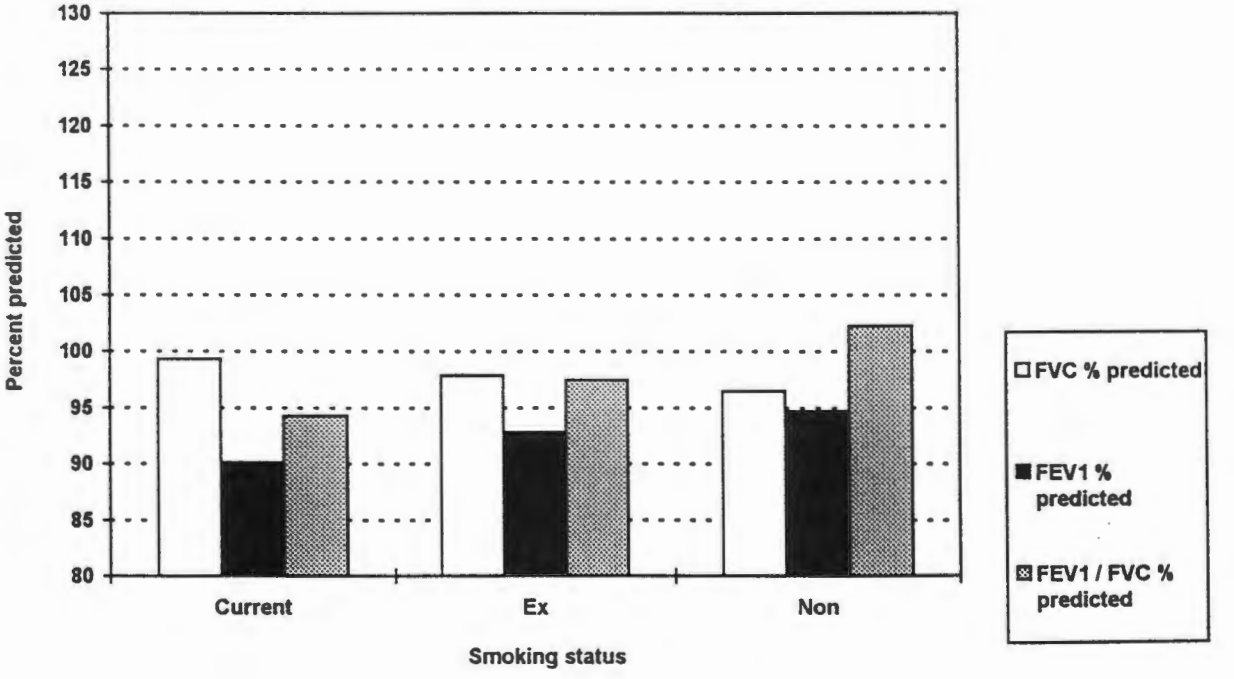


Figure 3.5 Pulmonary function findings among female grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

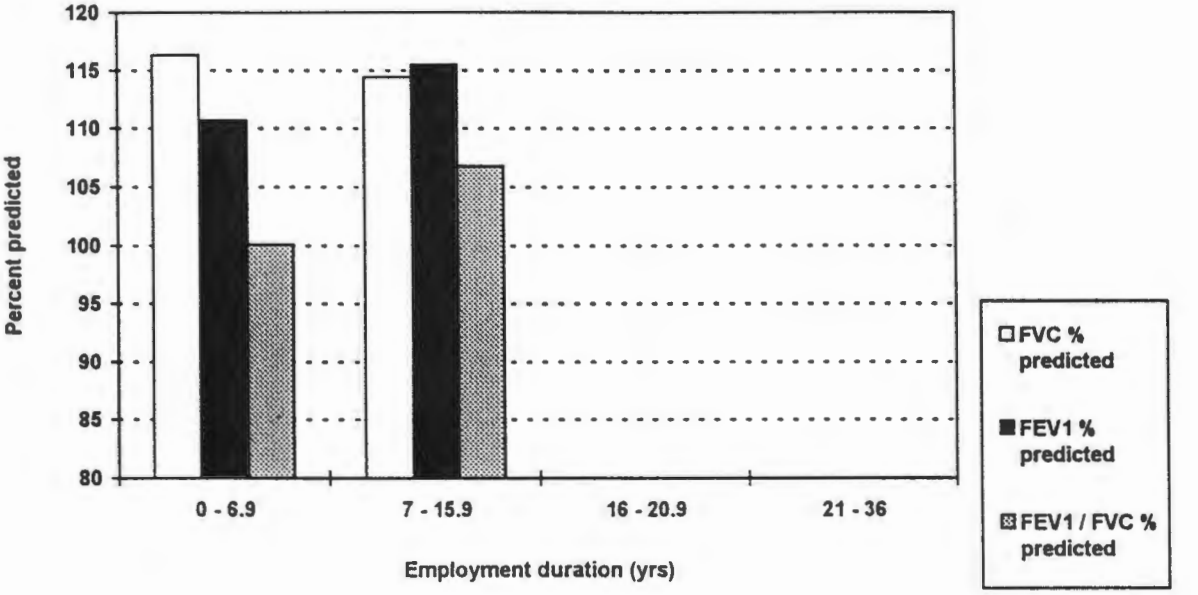
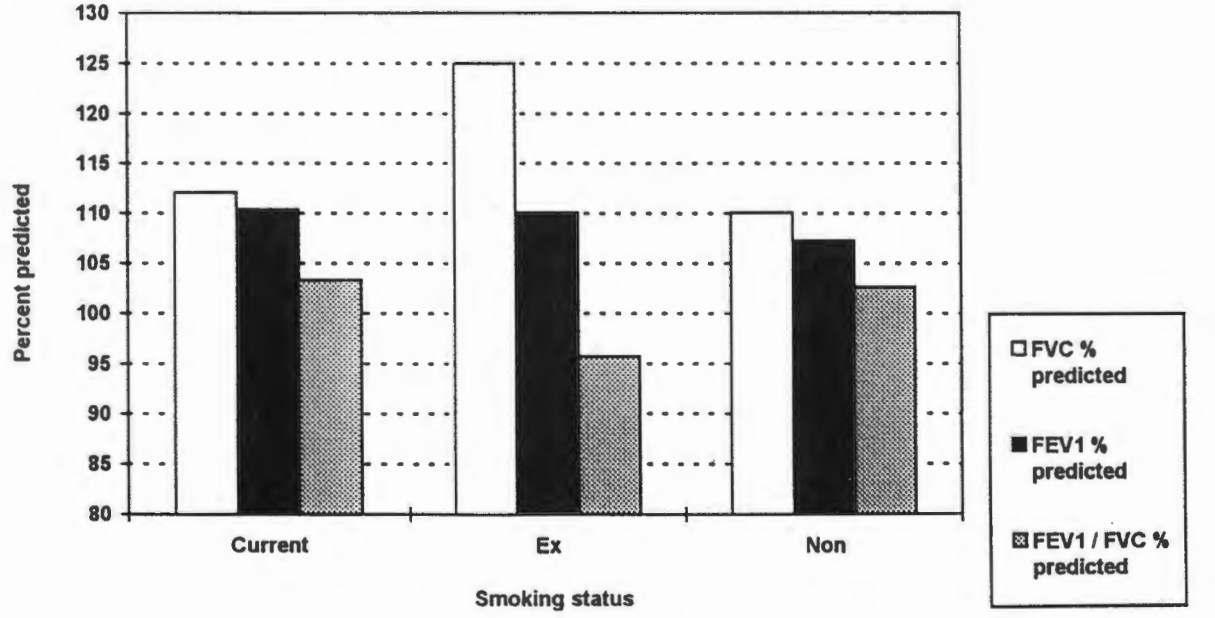


Figure 3.6 Pulmonary function findings among female grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status



Immunological tests

The mean ECP (geometric mean) levels of the entire workforce was 15.4 ± 2.5ug/l (Table 3.6). The trend in ECP levels increased with increasing employment duration (up to 21 years) and smoking status, but were not found to be significant (Table 3.7). Furthermore, although a negative correlation existed between ECP levels and lung function indices viz. FEV_1 (-0.11), FVC (-0.12) and FEV_1/FVC (-0.03), these were weak and not significant (Table 3.8). The prevalence of atopy (positive phadiotop test) in this working population was 45.3% and sensitisation to at least one occupational allergen (positive RAST ≥ grade 1) was 41.5%. The prevalences for sensitisation to individual occupational allergens was the highest for wheat (26.4%). This was followed by Tyrophagus putrescentiae (22.6%), rye (21.7%), Lepidopglyphus destructor (15.1%) and Sitophilus granarius (15.1%). No obvious trends were noted for either atopy, employment duration or smoking status. Similarly, no association could be demonstrated between sensitisation to any one of the occupational allergens and employment duration. There were however trends of increasing numbers of sensitised individuals to occupational allergens, notably for wheat and rye, with increasing smoking status. Significant associations ($p<0.05$) were demonstrated between smokers and nonsmokers for the storage mite, L. destructor, and the grain weevil, S. granarius. It is evident from Table 3.8 that very high linear correlations were found between wheat and rye ($r=0.92$) and L. destructor and T. putrescentiae ($r=0.85$).

Table 3.6 Immunological test findings of grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

		Employment duration (yrs)			
	Total (n=106)	1st Quartile (0-6.9 yrs) (n=26)	2nd Quartile (7-15.9 yrs) (n=27)	3rd Quartile (16-20.9 yrs) (n=26)	4th Quartile (21-36 yrs) (n=27)
ECP (ug/l)	15.4 ± 2.5	12.3 ± 2.1	17.4 ± 1.8	18.4 ± 2.7	14.2 ± 3.2
No. with ECP >15 ug/l	52 (48.1%)	8 (30.8%)	18 (66.7%)	13 (50%)	13 (48.1%)
Positive test results for:					
- Phadiotop	48 (45.3%)	14 (53.8%)	9 (33.3%)	12 (46.2%)	13 (48.1%)
- Wheat	28 (26.4%)	7 (26.9%)	4 (14.8%)	10 (38.5%)	7 (25.9%)
- Rye	23 (21.7%)	5 (19.2%)	4 (14.8%)	8 (30.8%)	6 (22.2%)
- Lepidoglyphus destructor	16 (15.1%)	3 (11.5%)	3 (11.1%)	6 (23.1%)	4 (14.8%)
- Tyrophagus putrescentiae	24 (22.6%	5 (19.2%)	5 (18.5%)	8 (30.8%)	6 (22.2%)
- Sitophilus granarius	16 (15.1%)	2 (7.7%)	2 (7.4%)	7 (26.9%)	5 (18.5%)
- One occupational allergen positive	44 (41.5%)	11 (42.3%)	9 (33.3%)	13 (50%)	11 (40.7%)

Note: Continuous variables - mean ± S.D.; Categorical variables - number (%)
For ECP: Geometric mean ± S.D.

Table 3.7 Immunological test findings of grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status

		Smoking status		
	Total (n=106)	Current (n=52)	Ex (n=31)	Non (n=23)
ECP (ug/l)	15.4 ± 2.5	18.0 ± 2.4	14.7 ± 2.3	11.6 ± 2.8
No. with ECP >15 ug/l	52 (48.1%)	30 (57.7%)	13 (41.9%)	9 (39.1%)
Positive test results for:				
- Phadiotop	48 (45.3%)	29 (55.8%)	10 (32.3%)	9 (39.1%)
- Wheat	28 (26.4%)	17 (32.7%)	7 (22.6%)	4 (17.4%)
- Rye	23 (21.7%)	14 (26.9%)	6 (19.4%)	3 (13.0%)
- Lepidoglyphus destructor	16 (15.1%)	12 (23.1%)	2 (6.5%)	2 (8.7%)*
- Tyrophagus putrescentiae	24 (22.6%)	15 (28.8%)	5 (16.1%)	4 (17.4%)
- Sitophilus granarius	16 (15.1%)	12 (23.1%)	2 (6.5%)	2 (8.7%)*
- One occupational allergen positive	44 (41.5%)	22 (42.3%)	12 (38.7%)	10 (43.5%)

Note: Continuous variables - mean ± S.D.; Categorical variables - number (%)
For ECP: Geometric mean ± S.D.
Mantel-Haenszel Chi-Square test: * p-value < 0.05

Figure 3.7 Immunological test findings of grain mill workers in Cape Town, South Africa, 1996, stratified according to employment duration

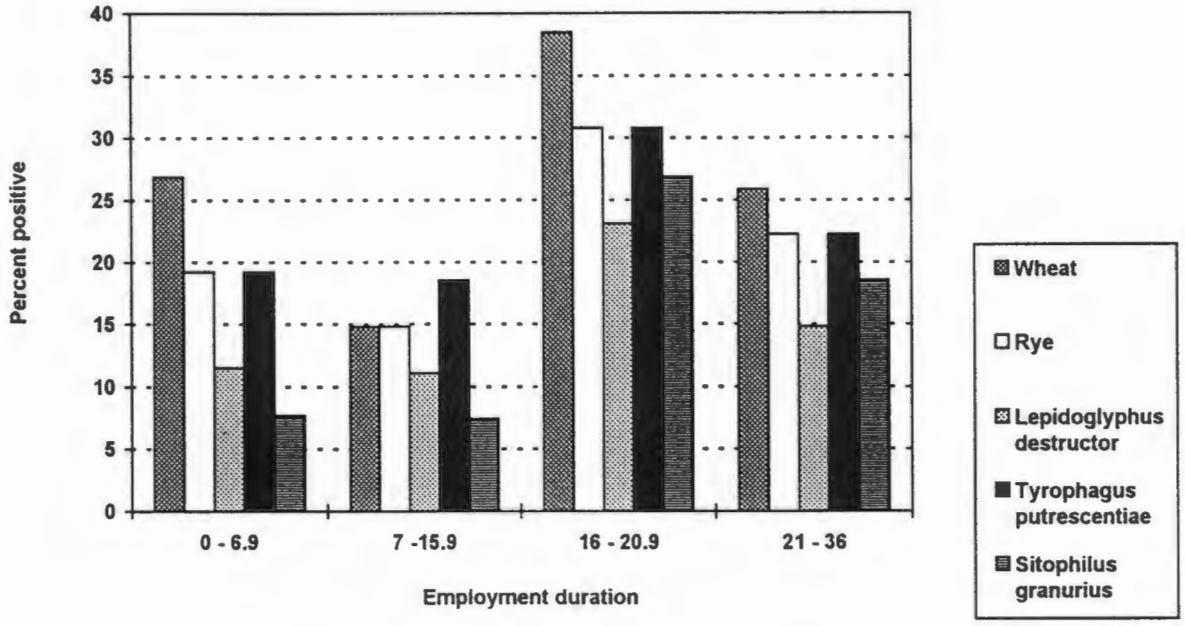


Figure 3.8 Immunological test findings of grain mill workers in Cape Town, South Africa, 1996, stratified according to smoking status

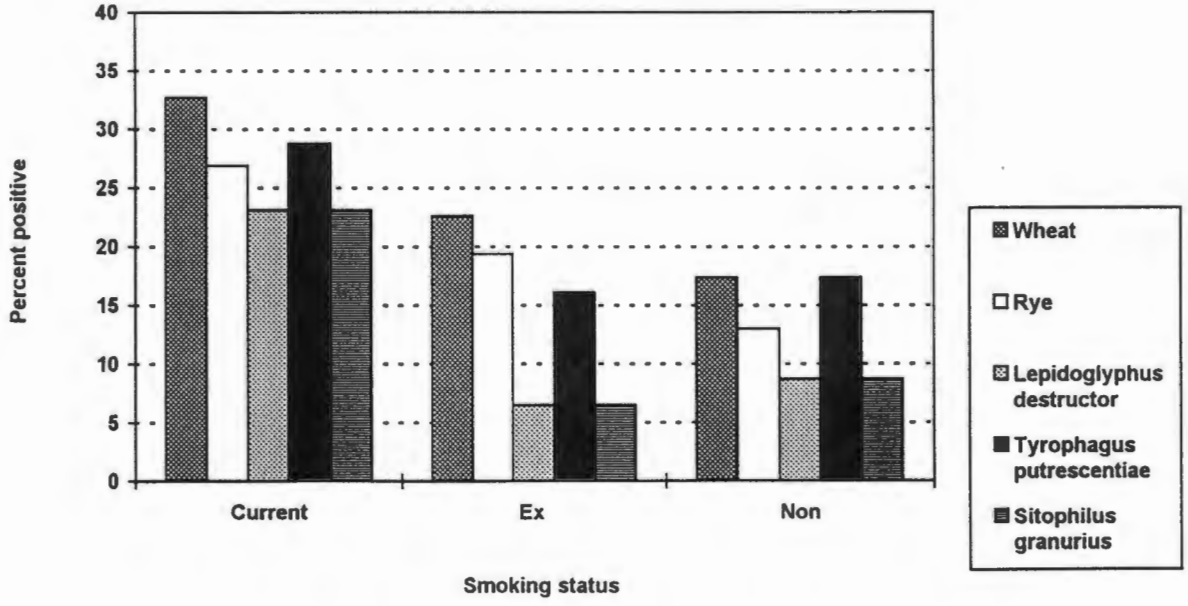


Table 3.8 Pearson Correlation Coefficients for covariates in grain mill study conducted in Cape Town, South Africa, 1996

Height	0.07														
Empl. duratn.	0.65***	0.01													
Dust conc.	0.23*	0.12	0.15												
Cum. exp. (log)	0.52***	0.06	0.65***	0.69***											
Smoking status	-0.05	-0.03	0.03	0.05	0.11										
Pack years	0.28	-0.09	0.14	-0.19	-0.04	0.21*									
FEV_1	-0.49***	0.42***	-0.43***	-0.02	-0.27**	-0.04	-0.17								
FVC	-0.31**	0.48***	-0.29***	-0.04	-0.17	0.08	-0.01	0.86***							
FEV_1/FVC	-0.44***	0.01	-0.36***	-0.01	-0.26**	-0.22*	-0.27*	0.53***	0.03						
ECP (log)	0.03	0.03	0.11	0.01	0.14	0.19*	-0.07	-0.11	-0.12	-0.03					
Wheat	0.13	-0.07	0.15	0.02	0.14	0.20*	0.04	-0.27**	-0.25*	-0.16	0.18				
Rye	0.19*	-0.10	0.17	-0.01	0.09	0.18	0.08	-0.31***	-0.31**	-0.19*	0.13	0.92***			
L. destruc.	0.07	-0.18	0.08	-0.15	0.01	0.12	-0.07	-0.15	-0.18	0.02	0.14	0.43***	0.42***		
T. putresc.	0.09	-0.11	0.10	-0.08	0.05	0.07	-0.05	-0.12	-0.18	0.05	0.15	0.47***	0.48***	0.85***	
S. gran.	0.20*	-0.18	0.23*	0.06	0.17	0.19*	-0.03	-0.24*	-0.25*	-0.07	-0.03	0.48***	0.49***	0.59***	0.56***
	Age	Height	Empl. duratn.	Dust conc.	Cum. expos. (log)	Smoke Status	Pack years	FEV_1	FVC	FEV_1/FVC	ECP (log)	Wheat	Rye	Lep. Destr.	Tyro. Putres.

Pearsons Correlation Coefficient: * p-value < 0.05; ** p-value < 0.01; ***p-value < 0.001

Dose response relationships - regression models

Linear regression models of ECP indicated a statistically significant association between sensitisation to wheat and ECP levels (Table 3.9). The estimated relationship between ECP and a positive wheat RAST was 1.78 ug/l (antilog 0.5737). Wheat RAST was also found to be an independent predictor of both FEV_1 and FVC after forcing employment duration into the model and adjusting for known confounders. Decrements of 278 ml in the FEV_1 and 328 ml in the FVC was associated with occupational sensitisation to wheat(rye). This is much greater than the mean decline of 18.3 ml in FEV_1 and 23 ml in FVC for every one year increase in employment duration. In assessing the change in lung function over the seven year period among the stayers, not much change had occured. In fact, there was an overall positive slope, indicating a mean increase in both FEV_1 of 2.9 ml/yr (SD:5.0) and FVC of 35.0 ml (SD:6.0). A negative slope in the FEV_1 over this period for increasing FEV_1 % change across the working week was also found. The estimated relationship of the slope in FEV_1 with the degree of obstruction (as determined by FEV_1/FVC ratio) was 0.1% per year. Furthermore, the FEV_1/FVC ratio was significantly ($p<0.001$) negatively correlated with reversibility after bronchodilator administration at the end of the working week for both FEV_1 ($r = -0.38$) and FVC ($r = -0.55$) in 1989.

Logistic regression functions were fitted for categorical outcomes listed in Table 3.10. Workers who were sensitised to wheat had almost threefold increased odds of having elevated ECP levels (OR=2.9) and smokers had a twofold increased odds of becoming atopic (OR=2.32). Atopy was also found to be the single most significant predictor of sensitisation to occupational allergens (lower 95% CI OR=8.9). For occupational asthma, age seemed to have a protective effect (OR=0.85), whereas employment duration (OR=1.35) and atopy (lower 95% CI OR=1.92) demonstrated an increased odds for being diagnosed with the disease.

Table 3.9 Regression models for immunological and pulmonary function test outcomes of grain mill workers in Cape Town, South Africa, 1996

Outcome	Model r^2	Independent variable	Regression Coefficient	Standard error	p-value
ECP (log)	0.0784	Intercept	2.5834	0.0991	0.0001
		Wheat RAST*	0.5737	0.1928	0.0036
FEV_1 (litres)	0.5365	Intercept	-3.5262	1.8683	0.0633
		Employment duration (yr)	-0.0183	0.0104	0.0826
		Age (yr)	-0.0357	0.0092	0.0002
		Height (cm)	0.0512	0.0107	0.0001
		Wheat RAST*	-0.2780	0.1476	0.0639
FVC (litres)	0.4578	Intercept	-4.2025	2.1019	0.0496
		Employment duration (yr)	-0.0230	0.0120	0.0597
		Age	-0.0249	0.0106	0.0214
		Gender**	0.5664	0.3020	0.0651
		Height (cm)	0.0550	0.0124	0.0001
		Wheat RAST*	-0.3282	0.1648	0.0505
FEV_1 slope over 7 yrs (litres/yr)	0.1909	Intercept	-0.0913	0.0504	0.0750
		% Δ FEV_1 across week	-0.0024	0.0007	0.0016
		FEV_1/FVC%	0.0011	0.0006	0.0956

* (1 = positive, 0 = negative), ** (1=male, 0=female)

Table 3.10 Logistic regression models for categorical outcomes among grain mill workers in Cape Town, South Africa, 1996

Outcome	Independent variable	Regression Coefficient	Standard error	p-value	OR	95% CI
ECP >15 (ug/l)	Intercept	-0.3102	0.2292	0.1760	-	-
	Wheat RAST*	1.0574	0.4650	0.0230	2.879	1.16-7.16
Atopy	Intercept	-0.6109	0.2850	0.0320	-	-
	Current smoker*	0.8427	0.3990	0.0347	2.32	1.06-5.08
Occupational allergy	Intercept	-3.4859	1.0082	0.0005	-	-
	Gender**	1.6305	0.9594	0.0892	5.11	0.78-33.48
	Phadiotop*	3.2470	0.5442	0.0001	25.71	8.85-74.71
Occupational asthma	Intercept	-1.0094	2.4065	0.6749	-	-
	Age (yr)	-0.1657	0.0836	0.0476	0.85	0.72-0.99
	Employment duration (yr)	0.2992	0.0995	0.0026	1.35	1.11-1.64
	Phadiotop*	2.5507	0.9649	0.0082	12.82	1.92-84.93
Chronic obstructive airways disease	Intercept	-6.2682	2.1707	0.0039	-	-
	Pack-years	0.1090	0.0599	0.0688	1.12	0.99-1.25

* (1 = positive, 0 = negative), ** (1=male, 0=female)

4. DISCUSSION

The results of this study indicate an association of grain dust with pulmonary function and allergic sensitisation to grain dust constituents. The proportion of workers with airway obstruction, in the bivariate analysis, increased significantly across increasing employment duration categories ($p<0.001$). After adjusting for known confounders such as age, gender and smoking using multivariate analysis, significant associations were found between employment duration (used as a proxy for exposure) and both decrements in lung function and sensitisation to wheat grain. A decrement of 278 ml in the FEV_1 and 328 ml in the FVC was associated with occupational sensitisation to wheat (and rye). Increasing employment duration resulted in annual decrements of 18.3 ml of FEV_1 and 23 ml in the FVC for every year employed. This study corroborates the findings of Sheridan et al who were also able to demonstrate an inverse relationship between employment duration and lung function. The odds for developing occupational asthma specifically was only mildly elevated (OR=1.35) with increasing employment duration. Age, however, was found to be protective (OR=0.85). This may be due to survivor effects operating, in that younger workers leave the job once they develop symptoms. The study by Broder et al showed an increase in acute symptoms among newly hired workers which were initially partly reversible when these workers were withdrawn from exposure.[82,38,11]

In this study three different models were initially developed to describe the associations between exposure and pulmonary function outcomes. Employment duration was finally chosen above dust concentration in current job category and cumulative dust exposure. Cumulative dust exposure is generally considered to be better than employment duration or dust concentrations because it is an integrated measure of both these variables. In our study, however, this measure was not as robust in predicting pulmonary outcomes due to possible exposure misclassification. Firstly, reliance was made on workers' personal recall of exposure histories rather than official employment records. Secondly, we used the dust concentrations obtained in 1989 as a surrogate measure of current job exposures instead of more recent measurements. Hence, the use of this model for characterising the effects on lung function, were not as significant for FEV_1 as those for FVC, leading to possible underestimation of exposure response relationships.[83,84,85]

This raises the possibility of selection effects that need to be considered. This is supported by the observation that the mean duration of employment in the higher dust concentration category was higher (9.1 yrs) than those in the low dust exposure category (8.9 yrs). The difference in prevalence of health outcomes has been documented previously in greater detail by Bachmann and Myers when they compared workers who had remained working in this mill in 1989 ("stayers") and those who had left the mill between 1983 and 1989 ("leavers"). It was found that the prevalence of all respiratory symptoms were higher among the "leavers" than among those who remained at the mill. This could therefore constitute a healthy worker survivor effect. Furthermore, the inability of Bachmann et al to demonstrate a decline in lung function across a seven year period was replicated by our study as well. Both studies were also unable to demonstrate that across-week changes in lung function, at inception, are related to rapid lung function decline. Tabona et al, on the other hand were able to show that across shift changes were related to longitudinal decline. One of the possible reasons for the discrepancy in these findings is that stronger selection effects may have been in operation in our study due to easier replacement of South African workers once they developed work-related health problems.[21,19]

Another plausible explanation for the failure to demonstrate an association between across-week changes and rapid lung function decline may be due to the fact that those workers who were unable to demonstrate a decline may have already had an element of fixed airway obstruction at the time when they were tested in 1989. Our study was able to demonstrate that longitudinal change in lung function was related to the degree of airway obstruction at inception. We were able to show that the degree of obstruction (FEV_1/FVC ratio) was significantly negatively correlated with reversibility after bronchodilator administration at the end of the working week for both FEV_1 ($r = -0.38$) and FVC ($r = -0.55$) in 1989. These findings suggest that across week reactions may be less sensitive than the across shift changes in predicting rapid longitudinal decline in lung function.[19,17]

Sensitisation to grain dust allergens was also found to be an independent predictor for respiratory health outcomes viz. FEV_1 and FVC. The prevalence of sensitisation was the highest for wheat (26.4%), followed by Tyrophagus putrescentiae (22.6%), rye (21.7%), Lepidoglyphus destructor (15.1%) and Sitophilus granarius (15.1%). A large proportion of the workforce (41.5%) were sensitised to occupational allergens, although the prevalence of respiratory symptoms was between

15.6% and 23.9% and only 7.3% of workers were being treated for asthma at the time of the study. This has been documented by Cullinan et al who were also only able to demonstrate a weak association between symptoms and specific sensitisation to grain dust allergens. Again, this could be due to selection effects operating viz. the healthy worker effect. Secondly, it could be due to under-diagnosis, since 16.7% fulfilled our criteria of occupational asthma. A third plausible explanation is that increased sensitisation only manifests as a particular disease entity such asthma in the presence of other host markers (those genetically determined) and host factors (those acquired) such as atopy or smoking,. Furthermore, exposure to acute peak dust concentrations and altered antigen presentation on subsequent occasions may also play a role. Differing allergenic potencies of antigens in terms of type of allergen (grain vs storage mite); route of exposure (inhalation vs ingestion) and cross-reactivity between antigens (wheat and rye) also become important. In our study sensitisation to wheat was highly correlated with sensitisation to rye (r=0.92) and so were Lepidoglyphus destructor and Tyrophagus putrescentiae (r=0.85). This suggests that they may have similar allergenic effects probably due to similar physical and biochemical properties.[86,87,88,5,10]

The study also tested the association between atopy, an important host factor, and observed respiratory health outcomes. The prevalence of atopy in this working population was relatively high (45.3%) when compared to a similar survey done in 1983 among grain mill workers in the Western Cape (22.4%). Atopic workers in our study had at least a nine-fold increased odds of becoming sensitised to grain dust allergens (OR: 8.9-74.7) and a two-fold increased odds of developing occupational asthma (OR=1.9-84.9). Atopy has been strongly associated with occupational asthma caused by high molecular weight agents, including the grain mites. However, the positive predictive value of a previous history of atopy or immediate skin reactivity to common allergens causing occupational asthma ranges from 8% to 34%, which is generally low. Malo and Chan-Yeung therefore correctly point out that the observed associations do not justify routine screening for atopy in high risk industries. They suggest that atopic workers intending to work in these industries be advised of this risk beforehand and that they have regular follow up to detect early sensitisation and non-specific bronchial responsiveness (NSBR).[20,36,37,89]

The effect of smoking on the lung function of these grain workers was also present. When stratified by smoking status, trends of declining lung function persisted with increasing smoking status for males. The proportion of workers with airway obstruction was significantly associated with smoking status among males ($p<0.05$). These findings corroborate those of Chan-Yeung et al and Cotton et al. The effects of smoking on occupational asthma appear to be dependent on the type of agent involved. It has been postulated that smoking increases the permeability of the respiratory epithelium among smokers, thus allowing greater penetration of antigens. Furthermore, our study found that smokers had a twofold increased odds of becoming atopic, thereby placing them at greater risk of developing respiratory health effects. This is consistent with the findings of Burrows et al who found that cigarette smoking increases serum IgE levels. Interestingly, smokers were more sensitised to the storage mites and grain weevil than to the grain allergens.[17,39,90,91]

This is the first study that has documented the prevalence of eosinophilic cationic protein (ECP) and its association with sensitisation to grain dust allergens in a working population. The mean ECP in this population was 15.4 ug/l (SD:2.5). This is much higher than the 11.3 ug/l found among patients in clinical settings or the suggested 15 ug/l cut-off for normal reference values in patient populations. The bivariate analysis showed that ECP levels increased with increasing employment duration and smoking status but this relationship was not significant. Although 45.3% of the workers were atopic, it was not found to be predictor of elevated ECP levels.[50]

In this study, we were able to demonstrate a significant association between ECP and sensitisation to grain allergens in a model which included age, gender, smoking status, employment duration, atopic status and the other grain dust allergens. Workers sensitised to wheat (positive RAST) had, on average, 1.78 ug/l higher ECP levels. Furthermore, the odds of having an elevated ECP (> 15 ug/l) increased by 2.9 for workers sensitised to wheat grain. These findings are to be expected since these workers are more likely to have increased circulating eosinophils and IgE. This suggests that ECP may be a better marker of exposure than employment duration or grain dust concentrations in air. This however does not explain the absence of a similar association between ECP and the other grain dust allergens eg. storage mites. Furthermore, although a negative correlation existed between ECP levels and lung function indices viz. FEV_1 (-0.11), FVC (-0.12) and FEV_1/FVC (-0.03), these were weak and not significant. These findings are not as convincing as those of Mapp et al who

demonstrated elevated ECP levels among a group of workers who developed a late asthmatic reaction when exposed to toluene diisocyanate (TDI) in a laboratory setting. This is due to the fact that the aspect of our study relating to the ECP component, being a cross-sectional observational design, had two major limitations. Firstly, we were unable to define the temporal sequence of events in this type of study design. Secondly, only once-off ECP levels were measured and no previous ECP levels were available to us for comparison. Therefore, we were unable to draw any conclusions on acute causal relationships between exposure, ECP and lung function changes.[51]

In conclusion, the specific contributions of this study relate to a detailed characterisation of the spectrum of allergic sensitisation in a group of grain mill workers in South Africa and its relationship to smoking and atopy. The findings suggest an important role of the wheat RAST as a tool in the surveillance of workers exposed to grain dust. A greater insight developed into understanding the relationship between the degree of reversible airway obstruction at baseline and future rapid lung function decline. This suggested that workers with pre-existing lung function abnormalities eg. tuberculosis needed to be regularly monitored once they joined the industry. It is apparent that more studies need to look into the utility of across-shift and across-week changes at baseline and their utility in predicting rapid lung function decline. The prevalence of ECP levels among working populations in general, and grain workers in particular has been described. Future studies need to focus on characterising the relationship between exposure to respiratory sensitisers such as grain dust, ECP levels and pulmonary function outcomes through stronger cohort study designs. In this manner, the role of ECP as an inflammatory marker in workers with occupational asthma can be more thoroughly evaluated in the workplace setting.

5. REFERENCES

[1] National Institute for Occupational Health and Safety (NIOSH). Work-Related Lung Disease Surveillance Report, 1996; Publication No.96-134.

[2] Meredith S. Reported incidence of occupational asthma in the United Kingdom, 1989-90. J Epidemiol Community Health 1993;47:459-463.

[3] Surveillance of Work-related and Occupational Respiratory Diseases in South Africa (SORDSA) News 1997;1(2).

[4] Chan-Yeung M, Kenedy S, Enarson DA. Grain Dust-Induced Lung Diseases. Asthma in the Workplace. Eds Bernstein IL, Chan-Yeung M, Malo JL and Bernstein DI. Marcel Decker Inc. 1993;27:577-594.

[5] Chan-Yeung M, Enarson DA, Kennedy SM. State of the art. The impact of grain dust on respiratory health. Am Rev Respir Dis 1992;145:476-487.

[6] Voorhorst RI, Spieksma FThM. Recent progress in the house dust mite problem. Acta Allergy 1969;24:115-21.

[7] do Picco GA, Jacobs S, Flaherty D, Rankin J. Pulmonary reaction to durum wheat: 1a constituent of grain dust. Chest 1982;81:55-61.

[8] Frankland AW, Lunn JA. Asthma caused by the grain weevil. Br J Ind Med 1965;22:157-9.

[9] Warren CPW. Overview of respiratory health risks in agriculture. In: Cockroft DW, Dosman JA, eds. Principles of health and safety in agriculture. Boca Raton, FL: CRC Press, 1990;47-9.

[10] O'Hollaren MT. Bakers' asthma and reactions secondary to soybean and grain dust. In: Bardanna EJ, Montanaro A, O'Hollaren AT, eds. Occupational asthma. Hanley & Belfus, Inc, 1992;107-116.

[11] Broder I, Mintz S, Hutcheon MA. Effect of lay-off and rehire on respiratory variables of grain elevator workers. Am Rev Respir Dis 1980;122:601-8.

[12] Corey P, Hutcheon M, Broder I, Mintz S. Grain elevator workers show work-related pulmonary function changes and dose effect relationships with dust exposure. Br J Ind Med 1982;39:330-7.

[13] do Picco GA, Reddan W, Anderson S, Flaherty D, Smalley E. Acute effects of grain dust exposure during a work shift. Am Rev Respir Dis 1983;128:399-404.

[14] Cockcroft AE, Mc Dermott M, Edwards JH, et al. Grain exposure - symptoms and lung function. Eur J Respir Dis 1983,63:189-196.

[15] Awad El Karim MA, Gad El Rab MO, Omer AA, et al. Respiratory and allergic disorders in workers exposed to grain and flour dusts. Arch Environ 1986;41:297-301.

[16] Enarson DA, Vedal S, Chan-Yeung M. Fate of grainhandlers with bronchial hyperreactivity. Clin Invest Med 1988,11:193-7.

[17] Chan-Yeung M, Shulzer M, MacLean L, Dorken E, Gryzbowski S. Epidemiologic health survey of grain elevator workers in British Columbia. Am Rev Respir Dis 1980;121:329-36.

[18] Chan-Yeung M, Schulzer M, MacLean L, et al. A follow up study of the grain elevator workers in the port of Vancouver. Arch Environ Health 1981;36:75-81.

[19] Tabona M, Chan-Yeung M, Enarson DA, MacLean L, Dorken E, Shulzer M. Host factors affecting longitudinal decline in spirometry among grain elevator workers. Chest 1984;85:782-6.

[20] Yach D, Myers J, Bradshaw D, Benetar SR. A respiratory epidemiologic survey of grain mill workers in Cape Town, South Africa. Am Rev Respir Dis 1985;131:505-10.

[21] Bachmann M, Myers JE. Grain dust and respiratory health in South African milling workers. Br J Ind Med 1991;48:656-662.

[22] Chan-Yeung M, Ward H, Enarson DA, Kennedy S. Five cross-sectional studies of grain-handlers in British Columbia (abstract). Am Rev Respir Dis 1991;143:A100.

[23] Moselhi M, El-Gazzar R, Abdul-Kader HM, El-Sadik YM. Clinical and biological investigations among grain handlers. J Egypt Public Health Assoc 1979;54:396-414.

[24] El Karim MAA, El Rab MOG, Omer AA, El Haimi YAA. Respiratory and allergic disorders in workers exposed to grain and flour dusts. Arch Environ Health 1986;41:297-301.

[25] Enarson DA, Chan-Yeung M. Rapid decline in FEV_1 in grain handlers: relation to level of exposure. Am Rev Respir Dis 1984;129:suppl A152.

[26] Kauffmann F, Drouet D, Lellouch J, et al. Occupational exposure and 12-year spirometric changes among Paris area workers. Br J Ind Med 1982;39:221-32.

[27] Cotton DJ, Graham BL, Li KYR, et al. Effects of grain dust exposure and smoking on respiratory symptoms and lung function. J Occup Med 1983;25:131-41.

[28] DoPico GA, Reddan W, Siatis A, et al. Epidemiologic study of clinical and physiologic parameters in grain handlers of Northern United States. Am J Respir Dis 1984;130:759-65.

[29] Dosman JA, Cotton DJ, Graham BL, et al. Chronic bronchitis and decreased forced expiratory flow rates in lifetime non-smoking grain workers. Am Rev Respir Dis 1980;121:11-6.

[30] Enarson DA, Chan-Yeung M, Tabona M, Kus J, Vedal S, Lam S. Predictors of bronchial hyperexcitability in grainhandlers. Chest 1985;87:452-5.

[31] Huy T, de Schipper k, Chan-Yeung M, et al. Grain dust and lung function. Am rev Respir Dis 1991;144:1314-21.

[32] Peelen S, Heederik D, Dimich-Ward H, et al. Comparison of dust related respiratory effects in Dutch and Canadian grain handling industries. Occup Env Med 1996;53:559-566.

[33] White N, Ehrlich R, Rees D. A guide to spirometry as applied to occupational health. S Afr Med J 1996;86:807-813.

[34] Dutch expert committee on occupational standards. A committee of the Health Council of the Netherlands. Health-based recommended occupational exposure limit for Grain dust. Draft, 1997.

[35] Heederik D, Kromhout H, Kromhout D, et al. Relations between occupation, smoking, lung function, and morbidity incidence and mortality of chronic non-specific lung disease: the Zutphen study. Br J Ind Med 1992; 49:299-308.

[36] Cuthbert OD, Brostoff J, Wraith DG, Brighton WD. "Barn Allergy": asthma and rhinitis due to storage mite. Clin Allergy 1979;9:229-36.

[37] Blainey AD, Topping MD, Ollier S, Davies RJ. Allergic respiratory disease in grainworkers. J Allergy Clin Immunol 1989;84:296-303.

[38] Broder I, Mintz M, Hutcheon P, et al. Comparison of respiratory variables in grain elevator workers and civic outsider workers of Thunder Bay, Canada. Am Rev Respir Dis 1979:119:193-203.

[39] Cotton DJ, Graham BL, Li KYR, Barnett GD, Dosman JA. Effects of smoking and occupational exposure on peripheral airway function in young cereal grain workers. Am Rev Respir Dis 1982;126:660-5.

[40] Enarson DA, Vedal S, Chan-Yeung M. Fate of grain handlers with bronchial hyperreactivity. Clin Invest Med 1988;11:193-7.

[41] Zejda JE, Pahwa P, Dosman JA. Decline in spirometric variables in grain workers from start of employment: differential effect of duration of follow up. Br J Ind Med 1992;49:576-80.

[42] Broder I, Corey P, Davies G, et al. Longitudinal study of grain elevator and control workers with demonstration of healthy worker effect. J Occup Med 1985;27:873-80.

[43] Enarson DA, Vedal S, Chan-Yeung M. Does methacholine provocation testing prospectively identify trend in FEV1 in grainhandlers. Am Rev Respir Dis 1986;134:suppl A263.

[44] Horne SL, Clarke ME, Barnett GD. Alpha-1-antitrypsin deficiency: its effect on pulmonary function in Saskatchewan grain buyers. In: Dosman JA, Cotton DJ, eds. Occupational pulmonary disease: focus on grain dust and health. New York: Academic Press, 1980:437-56.

[45] Chan-Yeung M, Ashley MJ, Corey P, Maledy H. Phenotypes and the prevalence of chest symptoms and lung function abnormalities in workers employed in dusty industries. Am Rev Respir Dis 1978;117:239-45.

[46] Venables KM, Farrer N, Sharp L, Graneek BJ, Newman Taylor AJ. Respiratory symptoms questionnaire for asthma epidemiology: validity and reproducibility. Thorax 1993;48:214-219.

[47] Warren CPW, Cherniak RM, Tse KS. Hypersensitivity to grain dust. J Allergy Clin Immunol 1974;53:139-49.

[48] Ahlstedt S. Inflammation markers in asthma - definition, interpretation and practical implications. Current Allergy and Immunology 1996;9(2):11-14.

[49] Venge P, Dahl R, Fredens K, Peterson CGB. Epithelial injury by human eosinophils. Am Rev Respir Dis 1988;138:54-57.

[50] Pharmacia. Asthma and serum ECP measurement - Extracts from recent research. Ref 52-5104-58/02, 94-06. Total communication 1993; 1-17.

[51] Mapp CE et al. ECP, histamine and tryptase in peripheral blood before and during inhalation challenge with toluene diisocyanate (TDI) in sensitised subjects. Clin Exp Allergy 1994;24:730-736.

[52] Wever AMJ, Wever-Hess J, Hengsgens HESJ, Hermans J. Serum eosinophilic cationic protein (ECP) in chronic asthma. Relationship to spirometry, flow-volume curves PC_{20}, and exacerbations. Respir Med 1994;88:613-621.

[53] Boner AL, Peroni DG, Piacentinni GL, Venge P. Influence of allergen avoidance at high altitude on serum markers of eosinophil activation in children with allergic asthma. Clin Exp Allergy 1993;23:1021-1026.

[54] Venge P, Dahl R, Peterson C. Eosinophil Granule Proteins in serum after allergen challenge of asthmatic patients and the effects of anti-asthmatic medication. Int Arch Allergy Appl Immunol 1988;87:306-312.

[55] Bosquet J et al. Eosinophylic inflammation in asthma. N Engl J Med 1990;323:1033-1039.

[56] Venge P. Henriksen J, Dahl R. Eosinophils in exercise-induced asthma. J Allergy Clin Immunol 1991;88:699-704.

[57] Zimmerman B, Lanner A, Enander I, Zimmerman RS, Peterson CGB, Ahlstedt S. Total blood eosinophils, serum eosinophil cationic protein, and eosinophil protein X in childhood asthma: Relation to disease status and therapy. Clin Exp Allergy 1993;23:564-570.

[58] Hedlin G, Ahlstedt S, Enander I, Hakansson L, Venge P. Eosinophil cationic protein (ECP), neutrophil chemotactic activity (NCA) and tryptase in serum before and during bronchial challenge in cat-allergic children with asthma. Pediatr Allergy Immunol 1992;3:144-9.

[59] Editorial. South Africa's milling industry. World Grain 1994;12 (4):7.

[60] Bachmann M. Respiratory health survey at Premier Milling, Salt River and Epping. Industrial Health Research Group, 1989.

[61] Premier Food Industries / Food and Allied Workers Union - Joint health and safety agreement, 1992.

[62] Bachmann M. Dust survey report: Premier Milling, Salt River and Epping. Industrial Health Research Group, 1989.

[63] Jeebhay MF. Report on respiratory health screening of Premier Food workers in Salt River and Epping plants, 1991.

[64] Jeebhay MF, Abdullah MF, Edwards D. Report on the respiratory health screening of Premier food workers. IHRG, 1993.

[65] Jeebhay MF. Follow up report on the respiratory health screening of Premier Grain Mill workers. IHRG, 1994.

[66] Jeebhay MF, Bachmann M, Abdullah MF. Predictors of longitudinal changes in lung function among grain mill workers in Cape Town. IHRG, 1994.

[67] Van Rensburg LJ. Occupational hygiene monitoring at Premier Milling. OHE Monitoring CC, 1996.

[68] Occupational Health and Safety Act No.85 of 1993. Government Gazette 1993; 337, No.14918.

[69] Regulations for Hazardous Chemical Substances, Government Gazette 1995; 362, No.16596.

[70] ACGIH. Threshold limit values 1992-1993. Cincinnati: ACGIH, 1992.

[71] Ehrlich R, Jeebhay MF. Occupational asthma. The ALLSA handbook of Practical Allergy. Allergy Society of South Africa, eds. Paul Potter and Steve Lee, Creda Press, Eppindust, 1994.

[72] Compensation for Occupational Injuries and Diseases Act No.130 of 1993. Government Gazette 1994; 340, No.15158.

[73] Rautenbach B. Permanent disability assessment in occupational diseases. Office of the Compensation Commissioner, Pretoria, in Occupational Health Southern Africa, 1996; 2:30-31.

[74] Ferris BG, Epidemiology standardisation project. Am Rev Respir Dis 1978;118:7-53.

[75] Gardner RM, Hankinson JL, West BJ, Clausen Jl, Crapo RO, Johnson RL, Epler GR. Standardisation of spirometry - 1987 update. Am Rev Respir Dis 1987;136:1285-98.

[76] Gardner RM, Hankinson JL, West BJ. Evaluating commercially available spirometers. Am Rev Respir Dis 1980;121:73-82.

[77] Vitallograph Limited. S-model spirometer. Operating and service manual. Buckingham: Vitallograph, 1982.

[78] Volmer WM, Johnson LR, McCamant LE, Buist AS. Longitudinal versus cross-sectional estimation of lung function decline - further insights. Statistics in Medicine 1988;7:685-696.

[79] Quanjer PhH, Tammeling JE, Cotes OF, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J 1993,6;(S)6:5-40.

[80] Leidel NA, Busch KA, Lynch JR. Occupational exposure sampling strategy manual. Washington, DC: US Government Printing Office, 1977,72.

[81] Seixas NS, Robins TG, Atfield MD, Moulton LH. Exposure -response relationships for coal mine dust and obstructive lung disease followng enactment of the federal Coal Mine Health and Safety Act of 1969. Am J Ind Med 1992;21:715-734.

[82] Sheridan D, Deutscher D, Tan L et al. The relationship between exposure to cereal grain dust and pulmonary function in grain workers. In: Dosman JA, Cotton DJ, red. Occupational pulmonary disease. Focus on grain dust and health. London: 1980:229-238.

[83] Seixas NS, Multon LH, Robins TG, Rice CH, Attfield MD, Zellers ET. Estimation of cumulative exposures for the national study of coalworkers pneumoconiosis. Appl Occup Environ Hyg 1991;6(12):1032-1041.

[84] Heederick D, Miller BG. Weak associations in occupational epidemiology: adjustment for exposure estimation error. Int J Epidemiol 1988;17(S):970.

[85] Armstrong BG, Oakes D. Effects of approximation in exposure assessments on estimates of exposure-response relationships. Scand J Work Environ Health 1982;8(S1):20.

[86] Cullinan P, Lowson D, Nieuwenhuijsen MJ, Sandiford C, Tee RD, Venables KM, Mc Donald JC, Newman Taylor AJ. Work-related symptoms, sensitisation, and estimated exposure in workers not previously exposed to flour. Occup Env Med 1994;51:579-583.

[87] Venables K. Epidemiology and prevention of occupational asthma (editorial). Br J Ind Med 1987;44:73-75.

[88] Vanhanen MV, Tuomi T, Hokkanen H, Tupasela O, Toumainen A, Holmberg PC, Leisola M, Nordman H. Enzyme exposure and enzyme sensitisation in the baking industry. Occ Env Med 1996;53:670-676.

[89] Jean-Luc Malo, Chan-Yeung M. Population surveys of occupational asthma. Asthma in the Workplace. Eds Bernstein IL, Chan-Yeung M, Malo JL and Bernstein DI. Marcel Decker Inc. 1993;8:145-170.

[90] Leskowitz S, Salvaggio JE, Schwarz HJ. An hypothesis for the development of atopic allergy in man. Clin Allergy 1972;2:237-246.

[91] Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. Am Rev Respir Dis 1981;124:523-529.

RESPIRATORY QUESTIONNAIRE FOR PREMIER MILLING - 1996

CARD [1]

A. IDENTIFICATION DATA

1. Surname _____ [23]
2. First name/s _____
3. Address _____ [25]
_____
_____
4. Work number _____ [4]
5. Date of birth Day ___ Month ___ Year 19 ___ [10]
6. Sex Male _____ (1) Female _____ (2) [27]
7. Shift 7am - 5pm (1) 2pm - 10pm (2) [11] [12] [13]
8. Interviewer's initials _____
9. Date of interview Day ___ Month ___ Year 19 ___ [19] [28]
10. Did you get tested and fill in a questionnaire in 1989?

YES (1) NO (2) [20]

have you changed your job in Premier since then?

YES (1) NO (2) [21]

[29]

APPENDIX 8.1

B. WORK HISTORY IN MILLING

I am going to ask you about your present work

1. How long have you been working at this mill/depot?

_____ years

2. What is your job here?

get a short description of the job

_____
_____

3. For how long have you been doing this job?

_____ years

4. Would you say that this job is:

give all options at once

Not dusty (1)
or Slightly dusty (2)
or Dusty (3)
or Very dusty (4)

5. Before doing this job at this mill/depot, did you do a different job here?

YES (1) NO (2)

If NO, skip to question 7.
If YES, continue with question 6.

6. What other jobs did you do here?

Start with the first job and work forward, getting a one line description of each job.

A. Job _____

How long did you do this job? _____ years

Was this job dusty?

YES (1) NO (2)

B. Job _____

How long did you do this job? _____ years

Was this job dusty?

YES (1) NO (2)

C. Job _____

How long did you do this job? _____ years

Was this job dusty?

YES (1) NO (2)

Check that the total number of years for the jobs is the same as the total years worked at the mill/depot - see Question 1.

7. Have you ever worked in other mills or bakeries?

YES (1) NO (2)

If NO, go straight to Section C

If YES, ask question 8.

CARD

8. Name the previous mills or bakeries:

	Name	From	To
a)	_____	19__	19__
b)	_____	19__	19__
c)	_____	19__	19__

C. HISTORY OF OTHER DUSTY JOBS

1. Have you ever worked with asbestos?

YES (1) NO (2)

If YES,

give the name of the business

_____

For how long did you work there? _____ years

get a one line description of the job

_____

2. Have you ever worked in a mine (other than an asbestos mine)?

YES (1) NO (2)

If YES,

give the name of the mine

_____

and type of dust _____

For how long did you work there? _____ years

get a one line description of the job

_____

3. Have you ever worked in a foundry?

YES (1) NO (2) |__|8

If YES,

give the name of the foundry _____

and type of dust _____

For how long did you work there? _____ years |__|__|10

get a one line description of the job

_____

4. Have you ever worked in a quarry?

YES (1) NO (2) |__|11

If YES,

give the name of the quarry _____

and type of dust _____

For how long did you work there? _____ years |__|__|13

get a one line description of the job

_____

5. Have you ever worked in any other place with dust, smoke or chemical fumes?

YES (1) NO (2) |__|14

If YES,

give the name of the place _____

and type of dust or chemical _____ _____

For how long did you work there? _____ years |__|__|16

get a one line description of the job

_____

|__|17

|__|18

|__|__|20

|__|__|22

|__|__|24

|__|25

D. SMOKING

1. Do you smoke?

YES (1) NO (2)

If YES, skip to Ques. 4

If NO, go on to Ques. 2

2. Have you ever smoked?

YES (1) NO (2)

If YES, go on to Ques. 3

If NO, skip to Ques 9

3. How long ago did you stop smoking?

a) less than 1 year (00)
b) ___ years (number)

go on to Ques. 4

4. For ex-smokers:

How many years did you smoke for? _____ years

For current smokers:

How many years have you smoked for? _____ years

5. Do/did you smoke:

give all the options at once

cigarettes (0)
or pipe only (1)
or cigarettes and pipe (2)

6. Cigarette smokers:
how many cigarettes do/did you smoke each day?

when person has answered, tick the correct block	
less than 10	(0)
between 10 and 19	(1)
between 20 and 30	(2)
more than 30	(3)

Pipe smokers:
how much pipe tobacco do/did you smoke in a week?

show different packets of tobacco

_____ grams

7. Do/did you inhale?

YES (1) NO (2)

E. RESPIRATORY HISTORY

I am now going to ask you some questions mainly about your chest.

COUGH

1. Do you usually cough when you wake up in the morning?

YES (1) NO (2)

2. Do you usually cough a lot during the day or night?

YES (1) NO (2)

If the answer to either Ques. 1 or Ques. 2 is YES, ask Ques. 3 and 4.

If the answer to both questions is NO, skip to the PHLEGM questions.

3. Do you cough like this on most days for as much as three months a year?

YES (1) NO (2)

26 29 30 31 32 33 34 35 36 37 38 39 40

4. Do you cough less on days when you are not at work?

YES (1) NO (2)

PHLEGM

1. Do you usually bring up phlegm from your chest when you get out of bed in the morning?

YES (1) NO (2)

2. Do you bring up phlegm for as much as three months a year?

YES (1) NO (2)

If the answer to either Ques 1 or Ques 2 is YES, ask Ques 3 and 4.

If the answer to both questions is NO, skip to the BREATHLESSNESS questions.

3. For how many years have you been coughing up this amount of phlegm?

_____ years

Write down number of years, then mark the correct block.

less than 2 years	(1)
more than 2 years	(2)

4. Do you bring up phlegm less on days when you are not at work?

YES (1) NO (2)

BREATHLESSNESS

1. Do you suffer from any shortness of breath?

YES (1) NO (2)

2. Do you suffer more from shortness of breath than other people of your own age?

YES (1) NO (2

3. Which of these activities make you feel short of breath?

Go through these one at a time.

running	(1)
heavy work	(2)
walking up a hill or up stairs	(3)
walking on flat ground	(4)
none of the above	(5)

Enter highest number here: ____ |__|41

4. Do you get less short of breath on days when you are not at work? |__|42

YES (1) NO (2)

TIGHTNESS

1. Does your chest ever feel tight or your breathing become difficult? |__|43

YES (1) NO (2)

If YES, carry on with Ques. 2 to 8

If NO, skip to Ques. 4

2. Is your chest less tight on days when you are not at work? |__|44

YES (1) NO (2)

3. Is your chest tight or your breathing difficult on any particular day of the week? |__|45

YES (1) NO (2)

If YES,

which day/s of the week is this usually? |__|46

Mon	Tues	Wed	Thur	Fri	Sat	Sun
1	2	3	4	5	6	7

|__|47

|__|48

|__|49

|__|50

|__|51

|__|52

Is this tightness worse:

	before work	(1)
or	during work	(2)
or	after work	(3)

4. Is there any food which makes your chest tight when you eat it?

YES (1) NO (2)

If YES,

what food? _____

5. Is there any drink that makes your chest tight when you drink it?

YES (1) NO (2)

If YES,

what drink? _____

6. Is there any substance that makes your chest tight when you breathe it?

YES (1) NO (2)

If YES,

what substance? _____

WHEEZING

1. Does your chest ever sound wheezy or whistling?

YES (1) NO (2)

2. Do you suffer from attacks of shortness of breath with wheezing?

YES (1) NO (2)

If the answer to either Ques 1 or Ques 2 is YES, ask Ques 3 - 10.

If the answer to both questions is NO, skip to Section F.

3. Do you get these attacks less often on days when you are not at work? |__| 53

YES (1) NO (2)

4. How many years ago did these attacks start? |__| 60

_____ years |__| 61

5. Do you still get these attacks? |__| 54

YES (1) NO (2)

6. Did you ever have these attacks before working in the mill/depot? |__| 55 |__| 62

YES (1) NO (2)

7. Are these attacks worse at any particular time of day? |__| 56 |3| |__| 1

YES (1) NO (2)

If YES,

are the attacks worse:

before work (1)
or during work(2)
or after work (3) |__| 57 |__|__| 3

8. Are these attacks worse on any particular day of the week? |__|__| 5

YES (1) NO (2) |__| 58

If YES,

mark the day: |__| 6

Mon Tues Wed Thur Fri Sat Sun |__| 7
1 2 3 4 5 6 7 |__| 59 |__| 8

9. Are these attacks worse during any particular season?

YES (1) NO (2)

If YES,

mark the season:

spring (1)
summer (2)
autumn (3)
winter (4)

10. When you are on holiday, do these attacks occur:

give options

as often as at work (1)
or less often than at work (2)
or more often than at work (3)

CARD

F. PAST ILLNESSES

1. How many days sick leave have you taken in the last month?

_____ days

If 0 days, skip Ques. 2

2. How many of these days were for chest illnesses?

_____ days

3. Have you ever been treated for:

TB	YES (1)	NO (2)	UNSURE (3)
hay fever	YES (1)	NO (2)	UNSURE (3)
asthma	YES (1)	NO (2)	UNSURE (3)

If the answer to asthma is YES, then ask the next two questions:

Did a doctor tell you that you had asthma?

YES (1) NO (2) |__| 9

Have you taken any medicine for asthma in the last month?

YES (1) NO (2) |__| 10

4. In the last 2 years, have you ever been treated in hospital for any chest problems?

List these problems only if the person does not know what chest problems you mean: TB, pneumonia, stabbed chest, chest operations, asthma, bronchitis

YES (1) NO (2) |__| 11

What was the problem?

_____

5. As a child, did you have any serious lung disease?

YES (1) NO (2) |__| 12

What was the disease?

_____

THANK YOU - THERE ARE NO MORE QUESTIONS!

MEDICAL DATA SHEET, PREMIER MILLING RESPIRATORY SURVEY - 1996

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

WORK NUMBER _____ |__|__|__| 15

HEIGHT _____ cm |__|__|__|__| 19

WEIGHT _____ kg |__|__|__|__| 23

CHEST EXAMINATION

NAD Abnormality |__| 24

If abnormality, give details

(Creps 1 / Wheezes 2 / Rhonchi 3 / Other 4) |__| 25

_____

_____

SPIROMETRY DATA SHEET, PREMIER MILLING RESPIRATORY SURVEY - 1996

A. IDENTIFICATION DATA

1. Surname _____

2. First name/s _____

3. Work number _____

4. Shift 7am - 5pm (1)
2pm- 10pm (2)

B. SPIROMETRY

Postshift pre-bronchodilator |__|__|__| 28

FVC

FEV1 |__|__|__| 31

FEV1 / FVC |__|__|__| 34

Spirometer number: _____ |__| 35

Postshift post-bronchodilator

FVC |__|__|__| 38

FEV1 |__|__|__| 41

FEV1 / FVC |__|__|__| 44

Spirometer number: _____ |__| 45

WORKERS' CLINIC

Industrial Health Research Group

WORKERS' CLINIC
Woodstock Community Health Centre
P. Bag 7, Woodstock 7915
Tel. (021) 47-8043

PR no. 1525972

MEDICAL SCREENING REPORT - PREMIER MILLING

NAME: _____

This is a report of the medical examination and tests conducted on you by medical staff from the Workers' Clinic during November/December 1996.

1. Medical examination: _____
2. Lung function tests: _____
3. Blood tests for allergy _____

COMMENTS:

- ☐ The results were normal. Since you are exposed to grain dust we recommend that you have regular medical surveillance.
- ☐ The results indicate that you have suspected/confirmed occupational asthma due to grain dust. Please make an appointment with the Workers' Clinic for further evaluation.
- ☐ The results indicate that you have chronic obstructive airways disease probably due to smoking.
- ☐ The results indicate that you have a general allergy. Consult your family doctor should you have symptoms of asthma.
- ☐ The results indicate early sensitisation to grain dust. Please make an appointment with the Workers' Clinic for further evaluation.

(Please note that the cross in the box applies to you)

Please do not hesitate to contact Sr Amina Mia or Sr Vivienne Stern at our clinic should you have any queries or require more detailed results of the investigations done on you.

Dr Mohamed Jeebhay, MBChB DOH
Workers' Occupational Health Clinic
Date: 18 August 1997

APPENDIX 8.2

GUIDELINE FOR ASSESSING AND MANAGING MEDICAL SURVEILLANCE RESULTS FROM PREMIER MILLING

1. Normal assessment

a) Criteria
- Normal LFT
- Negative phadiotop
- Negative RAST to grain dust allergens tested (wheat, rye, grain storage mites)

b) Management
- Regular biennial medical surveillance if working in any area besides admin dept viz. packing, warehouse, silo, rail, mill, maintenance, mill, bag store

2. Suspected occupational asthma due to grain dust

a) Criteria
- Positive RAST to grain dust allergens tested (wheat, rye, storage mites)
- Borderline/abnormal obstructive lung function test with reversibility
- Abnormal medical examination eg. wheeze
- (May have positive phadiotop)

b) Management
- If already diagnosed as having occupational asthma, continue follow up as usual
- If first presentation, worker takes results to Sr Amina Mia at the company clinic
- Sr Mia will make an appointment either at the Workers' Clinic or Occupational Diseases Clinic at Groote Schuur hospital to confirm diagnosis
- If Occupational asthma diagnosis confirmed:
  - Commence treatment if indicated
  - Submit claim to Compensation Commissioner (send Employer's Report to Sr Mia to complete)
  - Notify Dept of Labour
  - Notify company (through Sr Mia with regard to placement in areas of low/no exposure to grain dust)
    - Areas of high exposure (>4.0 mg/m^3): packing, warehouse, silo
    - Areas of low exposure (<4.0 mg/m^3): rail, maintenance, mill, bagstore
    - Areas of no exposure: admin, canteen, garage, delivery

3. Early sensitisation to grain dust

a) Criteria
- Positive RAST to grain dust allergens (wheat, rye, grain storage mites)
- No signs and symptoms of asthma
- Normal LFT
- (May have positive phadiotop)

b) Management
- If first presentation, worker takes results to Sr Amina Mia at the company clinic
- Sr Mia screens for symptoms of allergic conjunctivitis, rhinitis, dermatitis
- If symptoms present Sr Mia refers appropriately to confirm diagnosis and counsels worker regarding symptoms of asthma and adequate preventive measures

APPENDIX 8.3

4. Chronic obstructive airways disease probably due to grain dust exposure

a) Criteria
- Fixed airways obstruction
- Negative RAST test and phadiotop
- Negative smoking history (from questionnaire)
- No other significant lung disease (from questionnaire)

b) Management
- If first presentation, worker takes results to Sr Amina Mia at the company clinic
- If Mild/moderate: Sr Mia counsels patient regarding adequate preventive measures
- If Severe: Sr Mia will make an appointment either at the Workers' Clinic or Occupational Diseases Clinic at Groote Schuur hospital to confirm diagnosis
- If Severe chronic obstructive lung disease confirmed:
  - Counsel regarding adequate preventive measures
  - Notify company (through Sr Mia with regard to placement in areas of low/no exposure to grain dust)
    - Areas of high exposure (>4.0 mg/m^3): packing, warehouse, silo
    - Areas of low exposure (<4.0 mg/m^3): rail, maintenance, mill, bagstore
    - Areas of no exposure: admin, canteen, garage, delivery
- Consider medical boarding option with patient if no placement available

5. General allergy/atopy with or without asthma

a) Criteria
- Positive phadiotop and negative RAST to grain dust allergens
- Normal/borderline obstructive lung function test with/without reversibility

b) Management
- If first presentation, worker takes results to Sr Amina Mia at the company clinic or their own family doctor if they have symptoms of asthma
- Sr Mia counsels patient regarding adequate preventive measures, symptoms of occupational asthma, placement if appropriate (if exposed to areas of high dust exposure and becomes symptomatic)

6. Chronic obstructive airways disease probably due to smoking

a) Criteria
- Fixed airways obstruction
- Negative RAST test and phadiotop
- Significant smoking history (from questionnaire)
- No other significant lung disease (from questionnaire)

b) **Management**
- If first presentation, worker takes results to Sr Amina Mia at the company clinic
- Sr Mia counsels patient regarding smoking

HAZARDS OF GRAIN DUST

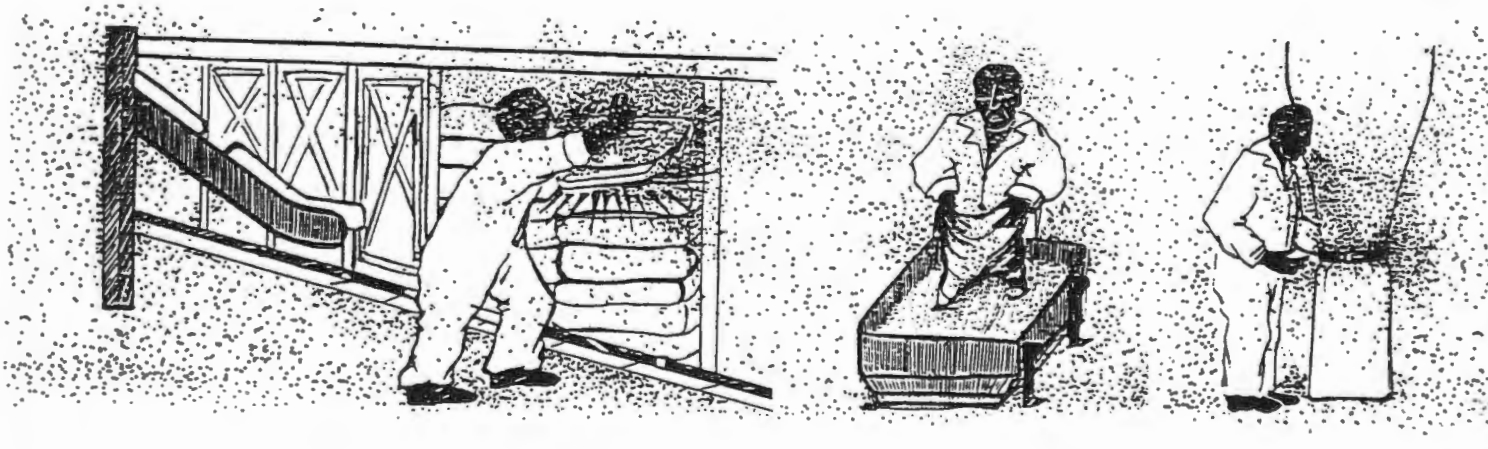
In the grain milling industry, workers grind maize, wheat and other grains to make flour. This work makes a lot of grain dust. If you breathe air which has grain dust in it, then you can get lung disease. After a long time in a dusty grain mill, your sickness can get very bad.

Small insects called weevils eat the grain and flour. Grain can also grow a fungus, and it can go mouldy. You can see this fungus on old bread. Chemicals are put into the grain or flour to kill insects and mould. When you breathe these in, you can also damage your lungs.

GRAIN AND FLOUR DUST AND YOUR HEALTH

Breathing dust

Self-raising flour has acid in it. If you get the dust from self-raising flour in your nose, it can burn your nose on the inside. Maybe your nose will also bleed.When you breathe, air goes down tubes inside your chest to your lungs. The tubes are called **bronchi**. Grain dust can damage these tubes on the inside, and give you **BRONCHITIS.** Your chest can hurt, and maybe you will cough up phlegm. If you have been working in grain dust for a short time, the bronchitis usually goes away after a few days.
If you have been working with the dust for a long time, you can have bronchitis all the time. This is called **CHRONIC BRONCHITIS**. With chronic bronchitis you can easily get short of breath, and maybe it will be hard for you to do a day's work. When this happens, your lungs never get better completely. The most common cause of this disease issmoking. You can get bronchitis from ordinary flour and self-raising flour, but self-raising flour is more dangerous.
ASTHMA is another sickness you can get from breathing grain and flour dust. This makes you short of breath like bronchitis. It also makes your chest whistle when you breathe. This is called wheezing. Your chest can feel tight. Doctors call this BAKER'S ASTHMA, because a lot of grain and flour workers get it. If you leave work for a few days, the baker's asthma can go away. But if you have had asthma for a long time, your chest may not get better.



HOW DO YOU KNOW IF THE GRAIN IS AFFECTING YOUR LUNGS?

You can get wheezing, coughing, shortness of breath, tight chest for many months, especially when you are working with the dust.

HOW CAN THESE HEALTH DANGERS BE PREVENTED?

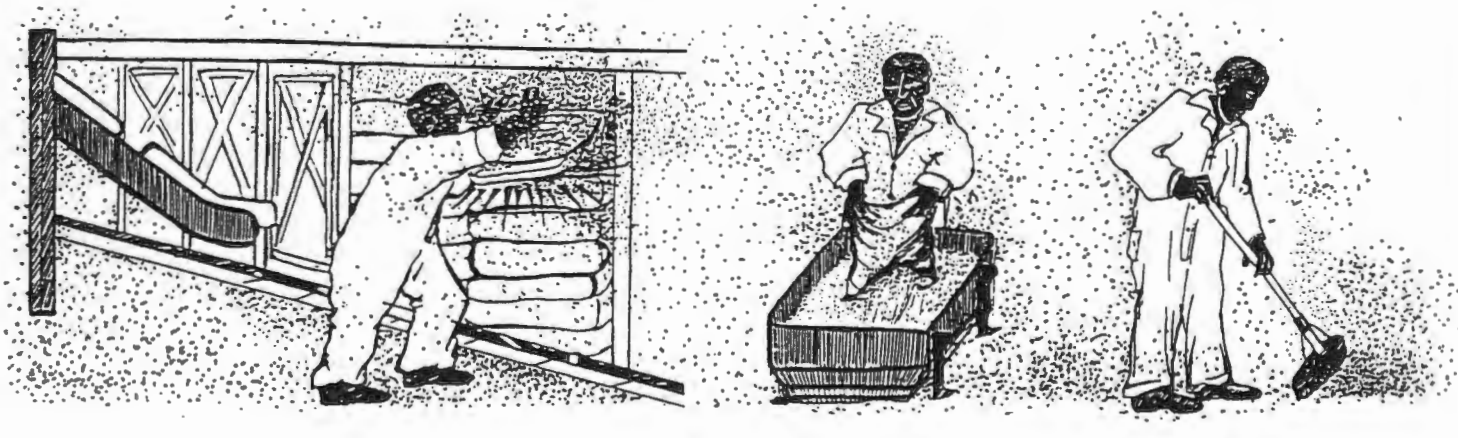
The main thing is to stop the grain dust getting to you.

HERE ARE SOME THINGS THAT CAN DO THIS

1. A CLEAN WORK ENVIRONMENT

Ventilation: You need ventilation that will suck the dusty air straight from the place where it is coming from. There is a hood over the dusty place, and a fan inside the pipe of the ventilation system sucks the air into the hood. This is called LOCAL EXHAUST VENTILATION, because the air is sucked from a small dusty area. Ordinary general ventilation does not help.

Enclosing machines: A dusty machine can be closed in a box so that the dust cannot get to you. The dust can be sucked away from inside the box by ventilation, so that it will never reach you. If you are working with a dusty, old machine, maybe there is a new machine that does the same job without the dust. You can try to get your employer to put in this new machine.



2. MEASURING THE GRAIN DUST

The air must be checked on a regular basis to make sure that the grain dust is being controlled effectively. There are international standards with which you can compare the dust in your mill. If the dust levels are too high, this will make workers sick.

3. PERSONAL PROTECTION

Personal protection means making workers wear special masks and goggles because they work in a very dusty factory. Masks are not as good for workers as ventilation, enclosure, changing the machines, or wetting the dust. Most masks do not work very well, and they are not comfortable.

If you wear a mask in a grain mill, you will know that the dust can still get into your nose and lungs. Masks are usually used in an emergency. For example, when the ventilation system is being fixed.

So masks are not the answer to dust.

4. REGULAR MEDICAL EXAMINATIONS

Workers in the grain industry should have regular medical examinations and lung function tests. It is also important to know that these tests will not make the factory safe. If a doctor sees you and finds that you have lung damage, it may be too late to do anything to stop the damage. If you have a medical examination before you start work in a dusty grain mill, and then every year while you work there, the doctor can tell you when you are starting to get sick, and you can get treatment or be removed from the very dusty areas. Those workers with asthma caused by grain dust can apply for workman's compensation to help them pay their medical bills and get compensation if they cannot work anymore.

5. EDUCATION AND TRAINING

All workers who work with grain dust must be properly trained so that they understand the risks and know how they should be protected against them.

Published by: Members of Industrial Health Research Group (IHRG), University of Cape Town